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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Pilot rapid assessment of pharmaceuticals using the HTA Core Model® for Rapid Relative Effectiveness Assessment

RAPID RELATIVE EFFECTIVENESS ASSESSMENT OF NEW PHARMACEUTICALS FOR THE TREATMENT OF CHRONIC HEPATITIS C

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals. This assessment was produced by experts from the institutions listed below, and was reviewed by members of Work Package 5 (WP5) Joint Action 2 of the EUnetHTA network; the whole process was coordinated by the Zorginstituut Nederland (ZIN).

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Conflict of interest

All authors and reviewers involved in the production of this pilot assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA conflicts of interest (COI) statement form.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
µg	Microgram
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ATC	Anatomical Therapeutic Chemical
CADTH	Canadian Agency for Drugs and Technologies in Health
CD	Cluster of differentiation
CENTRAL	Cochrane Central Register of Controlled Trials
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
COI	Conflicts of interest
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAAs	Direct-acting antivirals
DARE	Database of Abstracts of Reviews of Effects
DNA	Desoxyribonucleic acid
DRESS	Drug rash with eosinophilia and systemic symptoms
DSV	Dasabuvir
DCV	Daclatasvir
EASL	European Association for the Study of the Liver
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram

ELISA	Enzyme-linked immunoassay
EMA	European Medicines Agency
EPAR	European public assessment reports
EPCs	Evidence-based Practice Centres
EU	European Union
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitits C virus
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment (Database)
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
IDSA	Infectious Diseases Society of America
IDU	Intravenous drug users
IFN	Interferon
IL	Interleukin
Kg	Kilogram
LDV	Ledipasvir
LL	Lower limit
LVL	Low viral load
MAH	Market Authorization Holder
MeSH	Medical Subject Headings
Mg	Milligram
MSM	Men having sex with men
NMA	Network Meta Analysis

NR	Not reported
NS	Nonstructural protein
OBV	Ombitasvir
OCI	Occult hepatitis C infection
PBMC	Peripheral blood mononuclear cells
PDU	Parenteral drug users
PEG	Polyethylene glycol
Peg-IFN	Pegylated interferon
PI	Protease inhibitors
PICO	Patient-Intervention-Comparison-Outcome
PR	Pegylated interferon and ribavirin
PTV	Paritaprevir
PWID	People who inject drugs
QoL	Quality of life
RBV	Ribavirin
RCT	Randomised controlled trial
RD	Risk difference
REA	Rapid effectiveness assessment
RGT	Response-guided therapy
RIT	Ritonavir
RMP	Risk Management plan
RNA	Ribonucleic Acid
RR	Relative risk
SAE	Serious adverse event
Ser	Serine
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics

SMV	Simeprevir
SOF	Sofosbuvir
SR	Systematic review
SVR12	Sustained Virological response, defined as HCV-RNA below the quantifiable levels 12 weeks after the end of treatment
SVR24	Sustained Virological response, defined as HCV-RNA below the quantifiable levels 24 weeks after the end of treatment
T4	Thyroxin
TEL	Telaprevir
TEN	Toxic epidermal necrolysis
TID	Three times daily
TSH	Thyroid stimulating hormone
UK	United Kingdom
UL	Upper limit
US	United States
VA	Veteran affairs
VKH	Vogt-Koyanagi-Harada syndrome
WHO	World Health Organisation
WP5	Work Package 5

LIST OF TABLES AND FIGURES

SUMMARY OF RELATIVE EFFECTIVENESS OF NEW PHARMACEUTICALS FOR THE TREATMENT OF CHRONIC HEPATITIS C

SCOPE

To determine whether treatment with six new oral direct-acting antivirals (DAAs) (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in adults with chronic hepatitis C infection is more effective and safer than treatment with their comparators (the first generation DAAs: telaprevir and boceprevir, and the pegylated interferon [Peg-IFN] plus ribavirin combination regimen) and to each other.

INTRODUCTION

The hepatitis C virus (HCV), a ribonucleic acid (RNA) virus that caused the so-called non-A, non-B hepatitis infections, was discovered in 1989. HCV is a blood-borne virus that can be transmitted by contaminated needles or other material in a medical or non-medical setting. Currently, one of the main routes of infection in newly identified cases is through injection drug use. In particular, the sharing of needles and other materials has been associated with a high risk of transmission. People who inject drugs (PWID) are typically infected with HCV subtype 3a and, increasingly, subtype 1a. Over 80% of all new HCV infections in Western Europe are now seen in PWID, with the infection often occurring during the first year (or years) of injection drug use.

Another risk group identified in the recent years consists of human immunodeficiency virus (HIV)-positive men who have sex with men (MSM). HCV type 1 or 4 infections have been seen in patients coinfected with clinical syphilis and/or lymphogranuloma venereum rectitis. Medical procedures continue to account for about 10% of all new HCV infections. In infected women, transmission to the baby may occur at birth in 3–5% of cases, especially in the case of HIV-coinfection and a high HCV viral load. Finally, new HCV infections are also detected in first-generation immigrants from countries with a higher prevalence of HCV.

Treatments for hepatitis C were developed based on interferon-alpha (IFN-α) injections, which have a broad antiviral effect. Longer-acting formulations, such as pegylated IFN (Peg-IFN) and the addition of oral ribavirin improved efficacy. The efficacy endpoint in registration trials is a sustained virological response, defined as HCV RNA below the quantifiable levels 24 weeks after the end of treatment (SVR24). Using the combination of Peg-IFN plus ribavirin, up to 80% of patients with HCV genotype 2 or 3 infections (after 6 months of treatment), and 45% of those with genotype 1 infections (after 12 months of treatment) achieved SVR 24 weeks after the end of treatment in registration trials.

Fatigue and depression, which may already occur in treatment-naive patients with chronic hepatitis C, often worsen with Peg-IFN plus ribavirin treatment. These side-effects, together with the complex psychosocial state of the individual may hamper treatment uptake. For example, in the US only a third of patients infected with HCV were candidates for Peg-IFN-based treatment. Furthermore, patients for whom Peg-IFN was suitable might have elected not to pursue treatment to avoid potential side-effects. Overall, it has been estimated that less than 5–6% of infected patients had achieved SVR in the US in 2013.

New treatments for chronic hepatitis C

The long-awaited development of preclinical models has allowed for the selection of small molecules able to directly inhibit viral replication (directly acting antivirals [DAAs]). In patients with HCV genotype 1 infection, the addition of the protease inhibitor (telaprevir or boceprevir) to the Peg-IFN plus ribavirin regimen further improved the rate of SVR24 from 45% to 70%, and reduced the duration of treatment. Unfortunately, the incidence of the side-effects associated with this combination was higher than those of the standard Peg-IFN plus ribavirin combination.

The new-generation DAAs offer treatment options that are IFN-free, and sometimes even ribavirin. Combinations of the new-generation DAAs show very high SVR rates of up to 95%, are well tolerated, and reduce the duration of treatment even further (often to 12 weeks).

Because many patients are not eligible or are unwilling to be treated with Peg-IFN, it proved difficult to randomise patients to the standard treatment combination and a new DAA-based combination. In randomised-controlled trials (RCTs), patients were mainly randomised to treatment arms with different treatment durations, with and without ribavirin. Only a very limited number of studies were found that compared standard regimens with different DAA combinations. Therefore, many of the new trials are de facto single-arm trials.

We report SVR12 rates because SVR12 has replaced SVR24 as the primary efficacy endpoint in recent phase 2 and 3 clinical trials. SVR12 is an accepted but intermediate endpoint. Only a low proportion of patients will relapse after SVR12 or SVR24; for example in one study, 5 years following IFN-containing treatment, 4.7% of patients (95% confidence interval (CI) 2.0–7.4) had a relapse after SVR24. After SVR12 this proportion is likely to be 1–2% higher compared to SVR24. However, there are no long-term data available yet on the frequency of relapse after SVR12 following the new hepatitis C treatment combinations.

In the summary, we report only on the SVR12 rates for the European Association for the Study of the Liver (EASL)-recommended treatment options.

Description of Technology

The health technologies under assessment are the new-generation DAAs which recently received market authorisation for the treatment of chronic hepatitis C (CHC), namely: sofosbuvir; ledipasvir plus sofosbuvir; simeprevir; daclatasvir; ombitasvir plus paritaprevir plus ritonavir with or without dasabuvir; and/or combinations of these products in IFN-free or IFN-containing regimens.

We aimed to compare the new DAA treatment options with existing treatment options, including Peg-IFN-α-2a, Peg-IFN-α-2b, ribavirin, telaprevir, boceprevir, but also to compare them to each other.

The European Medicines Agency (EMA) indications for these DAAs in different hepatitis C virus genotypes are listed below. Details should be found in the Summary of Product Characteristic (SmPC) **(B0001, A0020)**.

Table S1. The European Medicines Agency (EMA) indications for DAAs in different genotypes

Drug	Indication	HCV Genotypes
Sofosbuvir	treatment of chronic hepatitis C (CHC) in adults in combination with other medicinal products (peginterferon alfa and/or ribavirin)	1 - 6
Ledipasvir + sofosbuvir	treatment of CHC in adults (with or without ribavirin)	1, 3, and 4
Simeprevir	treatment of CHC in adults in combination with other medicinal products (sofosbuvir with or without ribavirin or peginterferon alpha and ribavirin)	1 and 4
Daclatasvir	treatment of CHC infection in adults in combination with other medicinal products (sofosbuvir with or without ribavirin or peginterferon alfa and ribavirin)	1, 3, and 4
Ombitasvir + paritaprevir + ritonavir	treatment of CHC in adults in combination with other medicinal products (dasabuvir or ribavirin or both dasabuvir and ritonavir)	1a, 1b, and 4
Dasabuvir	treatment of CHC in adults in combination with other medicinal products (ombitasvir/ paritaprevir /ritonavir, with or without ribavirin)	1a and 1b

Peginterferon alfa-2a is a covalent conjugate of the protein interferon alfa-2a and polyethylene glycol (PEG) reagent. Peginterferon alfa-2b is a recombinant human interferon alfa-2b produced by recombinant DNA technology in *Escherichia coli*; recombinant interferon alfa-2b is covalently conjugated with monomethoxy PEG. Ribavirin is a synthetic nucleoside analogue.
Telaprevir is an inhibitor of the HCV NS3-4A serine protease, boceprevir is an inhibitor of the HCV NS3 protease, both from the previous generation of direct viral agents. Recently, in the United States (US) the Manufacturers of these two first generation DAAs voluntarily discontinued their manufacture and distribution **(B0001)**.

All new-generation DAAs are intended for oral use, all of them are taken once daily, except for dasabuvir which is taken twice daily. The comparators ribavirin, telaprevir, and boceprevir are also intended for oral use. Peg-IFN-α-2a and Peg-IFN-α-2b are administered by subcutaneous injection. For some genotypes, interventions such as sofosbuvir and simeprevir, even taken orally, may also be used with Peg-IFN-α: sofosbuvir in genotype 1, 3, 4, 5, or 6 and simeprevir in genotypes 1 and 4. Duration of treatment with interventions varies between 12 and 24 weeks; depending on the genotype and the presence or absence of cirrhosis **(B0001, B0002, A0002)**.

Pre-therapeutic assessment is an important part of the treatment. Before any treatment, all patients with HCV infection and a positive HCV RNA test result should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. All interventions and comparators should be initiated and monitored by a physician experienced in the management of patients with chronic hepatitis C; a multidisciplinary approach is required. Patient adherence to treatment must be assured **(B0004, B0008)**.

Health problem

HCV is an inflammation of the liver, which was isolated in 1989. Its transmission is primarily through exposure to infected blood. Risks for transmission have been identified **(A0003)**.

Infection with HCV is diagnosed by testing for specific antibodies using enzyme-linked immunoassay (ELISA) **(A0024)**. Within 7–21 days after viral transmission, HCV RNA becomes detectable in serum. HCV infection is infrequently diagnosed during the acute phase because of the lack of symptoms or the presence of non-specific symptoms and clinical signs **(A0002)**.

Chronic hepatitis C is marked by the persistence of HCV RNA in the blood for at least 6 months after the onset of acute infection. Chronic HCV can cause fibrosis, which can progress into liver cirrhosis, which could decompensate. HCC has been confirmed to be the prevalent complication. Chronic hepatitis C is also responsible for extrahepatic manifestations **(A0004)**, and HCV is associated with a higher risk of hospital admission **(A0005)**.

A clinical entity of interest, recently described, is occult hepatitis C infection (OCI), which is determined by the presence of HCV RNA in liver tissue or in peripheral blood mononuclear cells (PBMCs) occurring in an individual with undetectable HCV RNA in serum, in the absence or presence of anti-HCV antibodies **(A0004)**. The natural history of OCI is not yet fully defined.

Different estimates of HCV incidence in Europe are available. The overall prevalence of hepatitis C in Europe is estimated at 0.13–3.26% with an annual incidence rate of 6.19 per 100,000 inhabitants (95% CI 4.90–7.48) **(A0002)**. Variability in prevalence as in the distribution of HCV genotypes among countries is confirmed by many epidemiological studies. Many studies have estimated medical resource use and HCV-related costs in European countries **(A0006)**.

The target population is adult patients chronically infected with HCV genotype 1, 2, 3, 4, 5, or 6. Patients could be treatment-naive or treatment-experienced. International and national guidelines (Table A1, **A0025**) or recommendations could limit the target population or give priority to treatment of specific subgroups of patients **(A0025, A0023)**. The EASL guideline defines prioritisation criteria and therapies to adopt for different patient populations **(A0025)**. Estimates of the target population based on Eurostat data and published data, and prevalence data are reported in Table 3.5 **(A0023)**.

Heterogeneity in access to therapy among countries could be related to many causes such as restricted reimbursement, bureaucratic obstacles, exclusion from treatment of some patients (i.e. patients with mild hepatitis), ineffective therapy policies, and heterogeneity in screening for HCV **(A0011)**.

Data on diffusion of new DAAs is currently provisional and fragmented **(A0011)**.

METHODS

A systematic literature search (not limited by publication date) was performed according to EUnetHTA guidance on information retrieval in several databases, including MEDLINE, EMBASE,

and the Cochrane Library databases. Search date was November 2015. In addition, clinical trial registries were assessed and market authorisation holders were contacted.
The literature was selected independently by two reviewers. The study types included in the clinical effectiveness and safety domains focused on RCTs, prospective uncontrolled trials and prospective cohorts. In addition, for IFN-containing combinations in patients with genotype 1 HCV infection, we updated one systematic review of high quality, published by CADTH in October 2014.

The Cochrane Collaboration risk of bias concept was used (with some modifications because of the nature of the available evidence) to assess the quality of included studies. Furthermore, the AMSTAR tool was used to assess the quality of the CADTH systematic review. Risk of bias was evaluated independently by two authors. Data extraction was performed by one reviewer and double-checked by a second reviewer.

No quality assessment tool was used for the domains Description and Technical Characteristics of the Technology and Health Problem and Current Use of Technology, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis was performed on different information sources.

For the IFN-free combinations, the evidence did not allow either meta-analysis or network meta-analysis. The studies were either single-arm studies or randomised studies comparing different durations of the same treatment regimen with or without ribavirin. In the analysis, studies were treated as de facto single-arm studies and descriptive results with 95% CIs are shown for each study arm. For interferon containing combinations we updated a systematic review where a meta-analysis was possible.

RESULTS

Clinical Effectiveness

IFN-free combinations for treatment-naive non-cirrhotic patients with HCV genotype 1 infection

The results for IFN-free combinations for treatment-naive non-cirrhotic patients with HCV genotype 1 infection are shown in Table S2. As seen from the results, apart from the sofosbuvir plus ledipasvir 8-week combination regimen, all treatment arms have SVR12 rates above 95% and lower CIs above 90%. This means that the study can provide statistical evidence that the SVR12 is above 90%. Some differences exist in point estimates but the studies do not have the power to prove evidence that these differences are statistically different. Furthermore there are no direct comparisons between them.

Table S2. SVR12 in HCV genotype 1 treatment-naive patients.

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-1	ledipasvir + sofosbuvir	12	211	214	98,6 (96-99,7)
ION1	ledipasvir + sofosbuvir + ribavirin	12	211	217	97,2 (94,1-99)
ION-1	ledipasvir + sofosbuvir	24	212	217	97,7 (94,7-99,2)
ION-1	ledipasvir + sofosbuvir + ribavirin	24	215	217	99,1 (96,7-99,9)
LONESTAR	ledipasvir + sofosbuvir	8	19	20	95 (75,1-99,9)
LONESTAR	ledipasvir + sofosbuvir + ribavirin	8	21	21	100 (83,9-100)
LONESTAR	ledipasvir + sofosbuvir	12	18	20	90 (68,3-98,8)
Mizokami	ledipasvir + sofosbuvir	12	83	83	100 (95,7-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin	12	80	83	96,4 (89,8-99,2)

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
Osinusi	sofosbuvir + ribavirin patient weighted	12	17	25	68 (46,5-85,1)
Osinusi	sofosbuvir + ribavirin lower dose	12	12	25	48 (27,8-68,7)

IFN-free combinations for treatment-naive cirrhotic patients with HCV genotype 1 infection

The results for IFN-free combinations for treatment-naive cirrhotic patients with HCV genotype 1 infection are shown in table S3. Results show a tendency towards lower SVR12 than in non-cirrhotic patients, although CIs strongly overlap. All combinations have at least one study arm with a lower 95% CI that does not include a SVR of 75%.

Table S3. SVR12 in HCV genotype 1 treatment-naive patients with cirrhosis

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-1	ledipasvir + sofosbuvir	12	32	33	97 (84.2-99.9)
ION-1	ledipasvir + sofosbuvir + ribavirin (NE)	12	33	33	100 (89.4-100)
ION-1	ledipasvir + sofosbuvir	24	31	32	96.9 (83.8-99.9)
ION-1	ledipasvir + sofosbuvir + ribavirin (NE)	24	36	36	100 (90.3-100)
Mizokami	ledipasvir + sofosbuvir	12	13	13	100 (75.3-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	11	12	91.7 (61.5-99.8)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	12	81	86	94.2 (87-98.1)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	24	70	74	94.6 (86.7-98.5)
ELECTRON	ledipasvir + sofosbuvir	12	7	10	70 (34.8-93.3)
ELECTRON	ledipasvir + sofosbuvir + ribavirin (NE)	12	9	9	100 (66.4-100)
OPTIMIST 2	sofosbuvir + simeprevir	12	44	50	88 (75.7-95.5)

(NE) means that the duration or dose of this arm was not as recommended in the EPAR.

IFN-free combinations for treatment-experienced non-cirrhotic and cirrhotic patients with HCV genotype 1 infection

As EASL recommendations depend on the type of previous treatment, tables S4 and S5 show all summarized results independent from prior therapy. Table S4 considers patients with cirrhosis and Table S5 without cirrhosis. Overall, the results for treatment-experienced patients show a somewhat larger variability in SVR12 than the results for treatment-naive patients, although this could be due to random error since all ribavirin containing combinations have at least one study arm with a lower 95% CI that does not include a SVR of 75%.

Table S4. SVR12 in HCV genotype 1 treatment-experienced patients with cirrhosis

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-2	ledipasvir + sofosbuvir	12	19	22	86.4 (65.1-97.1)
ION-2	ledipasvir + sofosbuvir + ribavirin (NE)	12	18	22	81.8 (59.7-94.8)
ION-2	ledipasvir + sofosbuvir	24	22	22	100 (84.6-100)

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-2	ledipasvir + sofosbuvir + ribavirin (NE)	24	22	22	100 (84.6-100)
Mizokami	ledipasvir + sofosbuvir	12	28	28	100 (87.7-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	23	23	100 (85.2-100)
SIRIUS	ledipasvir + sofosbuvir + ribavirin (NE)	12	74	77	97.4 (90.9-99.7)
SIRIUS	ledipasvir + sofosbuvir	12	75	77	97.4 (90.9-99.7)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	12	110	122	90.2 (83.4-94.8)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	24	95	98	96.9 (91.3-99.4)
OPTIMIST-2	sofosbuvir + simeprevir	12	42	53	79.2 (65.9-89.2)

(NE) means that the duration or dose of this arm was not as recommended in the EPAR.

Table S5. SVR12 in HCV genotype 1 treatment-experienced patients without cirrhosis

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION - 2	ledipasvir + sofosbuvir	12	83	87	95.4 (88.6-98.7)
ION - 2	ledipasvir + sofosbuvir + ribavirin (NE)	12	89	89	100 (95.9-100)
ION - 2	ledipasvir + sofosbuvir	24	86	87	98.9 (93.8-100)
ION - 2	ledipasvir + sofosbuvir + ribavirin (NE)	24	88	89	98.9 (93.8-100)
Mizokami	ledipasvir + sofosbuvir	12	60	60	100 (94-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	64	64	100 (94-100)
SAPPHIRE-II	OBV/PTV/r + DSV + ribavirin	12	286	297	96.3 (93.5-98.1)
COSMOS	simeprevir + sofosbuvir + ribavirin	24	19	24	79.2 (57.8-92.9)
COSMOS	simeprevir + sofosbuvir	24	14	15	93.3 (68.1-99.8)
COSMOS	simeprevir + sofosbuvir + ribavirin	12	26	27	96.3 (81-99.9)
COSMOS	simeprevir + sofosbuvir	12	13	14	92.9 (66.1-99.8)
ELECTRON	sofosbuvir + ribavirin	12	1	10	10 (0.3-44.5)
Sulkowski	sofosbuvir + daclatasvir	24	21	21	100 (83.9-100)
Sulkowski	sofosbuvir + daclatasvir + ribavirin (NE)	24	19	20	95 (75.1-99.9)
OPTIMIST-1	simeprevir + sofosbuvir	12	38	40	95 (83.1-99.4)
OPTIMIST-1	simeprevir + sofosbuvir (NE)	8	40	52	76.3 (63.2-87.5)

(NE) means that the duration or dose of this arm was not as recommended in the EPAR.

IFN-free combinations for treatment-naive and/or treatment-experienced patients with HCV genotype 2 infection

For genotype 2, studies on sofosbuvir plus ribavirin show SVRs ranging from 86% to 100% in both treatment-naive and treatment-experienced patients independent of the cirrhosis status; all but one small study arm had a lower 95% CI that did not include a SVR12 of 70%.

Table S6. SVR12 results in HCV Genotype 2 patients

Study	Treatment combination	Duration of treatment (weeks)	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
POSITRON	sofosbuvir + ribavirin	12	Mix	101	109	92.7 (86-96.8)
FUSION	sofosbuvir + ribavirin	12	Mix	31	36	86.1 (70.5-95.3)
FUSION	sofosbuvir + ribavirin	16	Mix	30	32	93.8 (79.2-99.2)
Omata	sofosbuvir + ribavirin	12	Mix	148	153	96.7 (92.5-98.9)
Omata	sofosbuvir + ribavirin	12	Mix	88	90	97.8 (92.2-99.7)
Omata	sofosbuvir + ribavirin	12	Mix	60	63	95.2 (86.7-99.0)
Omata	sofosbuvir + ribavirin	12	Cirrhosis	16	17	94.1 (71.3-99.9)
VALENCE	sofosbuvir + ribavirin	12	Mix	68	73	93.2 (84.7-97.7)
BOSON	sofosbuvir + ribavirin	16	Mix	13	15	86.7 (59.5-98.3)
BOSON	sofosbuvir + ribavirin	24	Mix	17	17	100 (80.5-100)
FISSION	sofosbuvir + ribavirin	12	Mix	68	70	97.1 (90.1-99.7)

IFN-free combinations for treatment-naive and/or treatment-experienced patients with HCV genotype 3 infection

There is evidence only for the combinations sofosbuvir plus ribavirin and sofosbuvir plus daclatasvir. SVR12 rates are variable, with a tendency towards better results in treatment naive and non-cirrhotic patients compared to treatment-experienced cirrhotic patients, although there is no evidence that these differences are statistically significant.

Table S7. SVR12 results in HCV Genotype 3 patients

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
POSITRON	sofosbuvir + ribavirin (NE)	12	Mostly naive	Mix	60	98	61.2 (50.8-70.9)
FUSION	sofosbuvir + ribavirin (NE)	12	Experienced	Mix	19	64	29.7 (18.9-42.4)
FUSION	sofosbuvir + ribavirin (NE)	16	Experienced	Mix	39	63	61.9 (48.8-73.9)
VALENCE	sofosbuvir + ribavirin (NE)	12	Mix	Mix	3	11	27.3 (6-61)
VALENCE	sofosbuvir + ribavirin	24	Mix	Mix	213	250	85.2 (80.2-89.4)
VALENCE	sofosbuvir + ribavirin	24	Naive	No cirrhosis	87	92	94.6 (87.8-98.2)
VALENCE	sofosbuvir + ribavirin	24	Naive	Cirrhosis	12	13	92.3 (64-99.8)
VALENCE	sofosbuvir +	24	Experienced	No	85	98	86.7 (78.4-92.7)

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
	ribavirin			cirrhosis			
VALENCE	sofosbuvir + ribavirin	24	Experienced	Cirrhosis	29	47	61.7 (46.4-75.5)
VALENCE	sofosbuvir + ribavirin	24	Mix	No cirrhosis	173	190	91.1 (86.1-94.7)
VALENCE	sofosbuvir + ribavirin	24	Mix	Cirrhosis	41	60	68.3 (55-79.7)
BOSON	sofosbuvir + ribavirin (NE)	16	Mix	Mix	128	181	70.7 (63.5-77.2)
BOSON	sofosbuvir + ribavirin	24	Mix	Mix	153	182	84.1 (77.9-89.1)
BOSON	sofosbuvir + ribavirin (NE)	16	Naive	Mix	70	91	76.9 (66.9-85.1)
BOSON	sofosbuvir + ribavirin	24	Naive	Mix	83	94	88.3 (80-94)
BOSON	sofosbuvir + ribavirin (NE)	16	Naive	No cirrhosis	58	70	82.9 (72-90.8)
BOSON	sofosbuvir + ribavirin	24	Naive	No cirrhosis	65	72	90.3 (81-96)
BOSON	sofosbuvir + ribavirin (NE)	16	Naive	Cirrhosis	12	21	57.1 (34-78.2)
BOSON	sofosbuvir + ribavirin	24	Naive	Cirrhosis	18	22	81.8 (59.7-94.8)
BOSON	sofosbuvir + ribavirin (NE)	16	Experienced	Mix	58	90	64.4 (53.7-74.3)
BOSON	sofosbuvir + ribavirin	24	Experienced	Mix	70	88	79.5 (69.6-87.4)
BOSON	sofosbuvir + ribavirin (NE)	16	Experienced	No cirrhosis	41	54	75.9 (62.4-86.5)
BOSON	sofosbuvir + ribavirin	24	Experienced	No cirrhosis	44	54	81.5 (68.6-90.7)
BOSON	sofosbuvir + ribavirin (NE)	16	Experienced	Cirrhosis	17	36	47.2 (30.4-64.5)
BOSON	sofosbuvir + ribavirin	24	Experienced	Cirrhosis	26	34	76.5 (58.8-89.3)
FISSION	sofosbuvir + ribavirin (NE)	12	Naive	Mix	102	183	55.7 (48.2-63.1)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Naive	Mix	91	101	90.1 (82.5-95.1)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Experienced	Mix	44	51	86.3 (73.7-94.3)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Naive	No cirrhosis	73	75	97.3 (90.7-99.7)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Naive	Cirrhosis	11	19	57.9 (33.5-79.7)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Experienced	No cirrhosis	32	34	94.1 (80.3-99.3)
ALLY-3	sofosbuvir +	12	Experienced	Cirrhosis	9	13	69.2 (38.6-90.9)

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
	daclatasvir (NE)						

(NE) means that the duration or dose of this arm was not as recommended in the EPAR.

IFN-free combinations for treatment-naive and/or treatment-experienced patients with HCV genotype 4 infection

There is evidence for the combination OBV/PTV/r12 (without dasabuvir) with or without ribavirin; the combination with ribavirin shows a SVR12 of 100%, the lower 95% CI not including a SVR of 90% or less; the combination without ribavirin yields an SVR of 91% with the lower CI not including a SVR of 78%. Evidence for sofosbuvir plus ribavirin is mixed showing a tendency towards a lower SVR12, compared to combinations with 2 or more DAAs with the lower limit of the CI below 50%. Only one small study was found for ledipasvir plus sofosbuvir, showing a SVR12 of 95%, with a lower 95% CI not including a SVR12 of 75%.

Table S8. SVR12 results in HCV Genotype 4 patients

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
PEARL-I	OBV/PTV/r + DSV (NE)	12	Naive	No cirrhosis	40	44	90.9 (78.3-97.5)
PEARL-I	OBV/PTV/r + DSV + ribavirin	12	Naive	No cirrhosis	42	42	100 (91.6-100)
PEARL-I	OBV/PTV/r + DSV + ribavirin	12	Experienced	No cirrhosis	49	49	100 (92.7-100)
Ruane	sofosbuvir + ribavirin	12	Mix	Mix	21	31	67.7 (48.6-83.3)
Ruane	sofosbuvir + ribavirin	12	Naive	Mix	11	14	78.6 (49.2-95.3)
Ruane	sofosbuvir + ribavirin	12	Experienced	Mix	10	17	58.8 (32.9-81.6)
Ruane	sofosbuvir + ribavirin	24	Mix	Mix	27	29	93.1 (77.2-99.2)
Ruane	sofosbuvir + ribavirin	24	Naive	Mix	14	14	100 (76.8-100)
Ruane	sofosbuvir + ribavirin	24	Experienced	Mix	13	15	86.7 (59.5-98.3)
Kohli	ledipasvir + sofosbuvir	12	Mix	Mix	20	21	95.2 (76.2-99.9)

IFN-containing combinations for treatment-naive and treatment-experienced patients with HCV genotype 1 infection

The table below summarises the pairwise comparisons from the CADTH systematic review for patients with HCV genotype 1 treated with Peg-IFN-α plus ribavirin.

Table S9. Pairwise comparisons for genotype 1 with pegylated-interferon-alpha plus ribavirin (PR)

DAA vs. PR48	Population	N Trials	N Patients	SVR

				RD% (95%CI), I ² P	RR (95%CI), I ² P
simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Treatment naive	3	939	27 (18-35), 45	1.48 (1.25-1.75), 59
simeprevir for 12 weeks + PR for 48 weeks	Treatment experienced	1	132	44 (29-59), P<0.001	2.93 (1.82-4.72), P<0.001
simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Treatment experienced	1	393	42 (33-52), P<0.001	2.15 (1.71-2.71), P<0.001
sofosbuvir for 12 weeks + PR for 24 or 48 weeks RGT	Treatment naive	1	73	32 (11-53)	1.55 (1.10-2.18)

Abbreviations: RGT= response guided therapy PR=pegylated interferon + ribavirin

There is proof that SVRs are superior for simeprevir or sofosbuvir, each in combination with Peg-INF plus ribavirin, compared to Peg-IFN plus ribavirin alone.

In our update of the CADTH systematic review we found one study comparing simeprevir plus Peg-IFN and ribavirin, with telaprevir plus Peg-IFN and ribavirin with subgroup analysis for subtype and cirrhotic state. SVR12 rates were similar in both groups and ranged between 35% and 64% in the simeprevir group and between 37% and 67% and in the telaprevir group.

Table S10. SVR12 after PR-based combinations in HCV Genotype 1 – overall and subgroups

Study	Treatment combination	Genotype/ subtype	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ATTAIN	telaprevir for 12 weeks + PR for 48 weeks	1	Mix	210	384	54.7 (49.6-59.7)
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1	Mix	203	379	53.6 (48.4-58.7)
ATTAIN	telaprevir for 12 weeks + PR for 48 weeks	1a	Mix	63	164	38.4 (30.9-46.3)
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1a	Mix	66	164	40.2 (32.7-48.2)
ATTAIN	telaprevir for 12 weeks + PR for 48 weeks	1b	Mix	147	220	66.8 (60.2-73)
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1b	Mix	137	215	63.7 (56.9-70.2)
ATTAIN	telaprevir for 12 weeks + PR for 48	1	Cirrhosis	19	51	37.3 (24.1-51.9)

	weeks					
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1	Cirrhosis	20	57	35.1 (22.9-48.9)

Abbreviations: PR=pegylated interferon + ribavirin

IFN-containing combinations for treatment-naive and treatment-experienced patients with HCV genotype 2, 3, or 4 infection

Table S11. SVR12 after PR-based combinations in HCV Genotype 2– overall and subgroups

Study	Treatment combination	Treatment Status	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Mix	22	23	95.7 (78.1-99.9)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	No cirrhosis	9	9	100 (66.4-100)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Cirrhosis	13	14	92.9 (66.1-99.8)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Mix	Mix	15	16	93.8 (69.8- 99.8)
Dore	daclatasvir for 12 weeks + PR for 12 or 24 weeks RGT	Naive	No cirrhosis	21	24	87.5 (67.6-97.3)
Dore	daclatasvir for 16 weeks + PR for 16 or 24 weeks RGT	Naive	No cirrhosis	19	23	82.6 (61.2-95)
Dore	PR for 24 weeks	Naive	No cirrhosis	17	24	70.8 (48.9-87.4)

Abbreviations: RGT= response guided therapy PR=pegylated interferon + ribavirin

Table S12. SVR12 after PR-based combinations in HCV Genotype 3 – overall and subgroups

Study	Treatment combination	Treatment Status	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Mix	20	24	83.3 (62.6-95.3)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	No cirrhosis	10	12	83.3 (51.6-97.9)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Cirrhosis	10	12	83.3 (51.6-97.9)

BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Mix	Mix	168	181	92.8 (88-96.1)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Naive	Mix	89	94	94.7 (88-96.1)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Naive	No cirrhosis	68	71	95.8 (88.1-99.1)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Naive	Cirrhosis	21	23	91.3 (72-98.9)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Mix	79	87	90.8 (82.7-95.9)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	No cirrhosis	49	52	94.2 (84.1-98.8)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Cirrhosis	30	35	85.7 (69.7-95.2)
Dore	daclatasvir for 12 weeks + PR for 12 or 24 weeks RGT	Naive	Mix	18	26	69.2 (48.2-85.7)
Dore	daclatasvir for 16 weeks + PR for 16 or 24 weeks RGT	Naive	Mix	21	27	77.8 (57.7-91.4)
Dore	PR for 24 weeks	Naive	Mix	14	27	51.9 (31.9-71.3)

Abbreviations: RGT= response guided therapy PR=pegylated interferon + ribavirin

Table S13. Genotype 4– overall and in subgroups

Study	Treatment combination	Previous Treatment Status	Fibrosis status	Other	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
COMMAND	20mg daclatasvir for 12 weeks + PR for 12 weeks	Naive	Mix	SVR24	8	12	66.7 (34.9-90.1)
COMMAND	60mg daclatasvir for 12 weeks + PR for 12 weeks	Naive	Mix	SVR24	12	12	100 (73.5-100)
RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Mix	Mix		70	107	65.4 (55.6-74.4)

RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Naive	Mix		29	35	82.9 (66.4-93.4)
RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Experienced	Cirrhosis	Relapser	19	22	86.4 (65.1-97.1)
RESTORE	simeprevir for 12 weeks + PR for 48 weeks	Experienced	Cirrhosis	Non-Relapser	22	50	44 (30-58.1)
RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Experienced	Cirrhosis		13	28	46.4 (27.5-66.1)

Abbreviations: RGT= response guided therapy PR=pegylated interferon + ribavirin

In summary, IFN-containing regimens show variable effectiveness overall and in subgroups, numbers are small and 95% CIs are wide.

Special subgroups

SVR12 rates were similar in HIV-infected patients compared to non-HIV-infected patients. SVR12 was also similar in pre- and post-transplant patients in the few studies on this topic.

Other outcomes

There is no direct evidence from RCTs on the outcomes of mortality or long-term relapse, because studies had a short follow-up period. The effect of treatment on these outcomes can only be extrapolated from the indirect evidence of a residual disease progression as observed after treatments that have been on the market for a longer period. Data on quality of life during and shortly after treatment show that interferon-free combination provoke a small decrease in quality of life during treatment and a small improvement after SVR.

Safety

The primary safety outcomes were frequency of adverse events (AEs): any AEs, serious AEs (SAEs), most frequent AEs, and discontinuation due to AEs. There were no randomised or other studies that directly (head-to-head) compared the second-generation DAA oral therapies that are currently under assessment. The majority of the studies compared different dosing regimens of the same drug combinations to each other but not to older therapies like PR or PR plus one of the first generation protease inhibitors. The lack of head-to-head clinical trials and the availability of only single-arm studies makes it difficult to compare the safety of the different treatment regimens. Data for HCV genotypes 5 and 6 were insufficient for any conclusions to be drawn. Data were limited for patients with HIV-coinfection and pre- and post-liver-transplant patients.

In April 2015, after marketing authorisation, the European Medicines Agency (EMA) recommended avoidance of certain hepatitis C medicines and amiodarone together because **c**oncomitant use may increase risk of slow heart rate and related problems. EMA has confirmed a risk of severe bradycardia or heart block when the hepatitis C medicines sofosbuvir+ledipasvir or a combination of sofosbuvir and daclatasvir are used in patients who are also taking the medicine amiodarone **(B0001**).

After marketing authorisation cases of hepatic decompensation and hepatic failure, including fatal cases have been reported during treatments with simeprevir in combination with peginterferon

alfa and ribavirin or in combination with sofosbuvir. Most cases were reported in patients with advanced and/or decompensated cirrhosis who are at increased risk for hepatic decompensation or hepatic failure. In October 2015, US Food and Drug Administration (FDA) announced a warning for ombitasvir + paritaprevir + ritonavir tablets co-packaged with dasabuvir, and for ombitasvir + paritaprevir + ritonavir treatment; serious liver injury were reported, mostly in patients with underlying advanced liver disease, some resulted in liver transplantation or death **(B0001)**.

IFN-containing regimens: simeprevir and sofosbuvir in patients with HCV genotype 1 infection

The findings for treatment-naive, treatment-experienced, and combined patients on sofosbuvir plus simeprevir, each in combination with Peg-IFN plus ribavirin for genotype 1 hepatitis C infection were similar in terms of AEs; the overall AE profile in patients treated with simeprevir in combination with Peg-IFN plus ribavirin was comparable to that in patients who received Peg-IFN plus ribavirin alone. The three most frequent AEs in both groups were neutropenia, anaemia, and rash. The rates of discontinuation of simeprevir and Peg-IFN plus ribavirin were similar between the simeprevir and Peg-IFN plus ribavirin combination group and the Peg-IFN plus ribavirin group; the same was true for SAEs. No new comparative data were available for sofosbuvir plus Peg-IFN plus ribavirin versus Peg-IFN plus ribavirin alone **(C0008a, C0008b)**.

One head-to-head study compared simeprevir (12 weeks) plus Peg-IFN plus ribavirin (48 weeks) and telaprevir (12 weeks) plus Peg-IFN plus ribavirin (48 weeks) in treatment-experienced patients. Differences were recorded between treatment groups in SMV- or telaprevir-related AEs (69% in the SMV+PR group vs 86% in the telaprevir+PR group), SAEs (2% vs 9%), and AEs leading to study drug discontinuation (2% vs 8%). The most frequent AEs in the SMV+PR group were pruritus (32%), rash (21%), and neutropenia (18%); in in the telaprevir+PR group, the most frequent AEs were pruritus (44%), rash (31%), and anaemia (38%) **(C0008a, C0008b)**.

Interferon-containing regimens for genotypes 2 to 6 HCV infection

Frequency of any AEs reported with three DAAs + PR regimen in genotypes other than genotype 1 (total of six studies found on SOF, SMV and DCV) was within the range of 70%-99%, SAEs were reported with frequency of 4.7%-9%. The most frequent AEs across all studies were headache, fatigue and insomnia, and in HIV confection patients, anaemia and neutropenia (52%-57%).

Interferon-free regimens for genotype 1 to 6 HCV infection

AEs were frequently reported (within the range of 40%-100%) across all treatments with new oral DAAs under assessment and all genotypes. Discontinuations due to AEs were reported infrequently. SAEs were reported with a frequency of 1%-10%. The most common AEs reported for the new oral drugs under assessment (in treatment-naive, treatment-experienced, and combined patient groups) were headache, fatigue, insomnia, and nausea. In treatment regimens with Peg-IFN plus ribavirin, the most common AEs were rash, neutropenia, and anaemia **(C0008a, C0008b)**.
In two clinical studies on OBV12+PTV12+RIT12+DSV12 with or without ribavirin, some AEs occurred at a statistically higher frequency among patients who received ribavirin than among those who did not. In one study pruritus, nausea and insomnia (P=0.02); in the other study fatigue, nausea, insomnia, anemia, rash, increased blood bilirubin levels, and low haemoglobin levels (P<0.001-0.017) **(C0008a, C0008b)**.

Safety profiles were not related to dosage or frequency or administration and did not change over the observed time period of 12 or 24 weeks for the majority of new DAAs under assessment, with the exception of two studies**.** Among patients who received ledipasvir plus sofosbuvir alone, the incidence of AEs was higher in the 24-week group than in the 12-week group (81% vs 67%). Statistically significant differences were found for the combination of ombitasvir plus paritaprevir plus ritonavir plus dasabuvir (OBV+PTV+RIT+DSV) + ribavirin: fatigue and dyspnoea were statistically significantly higher in the group of patients treated for 24 weeks **(C0002, C0004)**.

According the susceptible patient groups that are more likely to be harmed, few studies were found in HIV co-infected and pre or post liver transplanted patients.

AEs were common with HIV-co-infection, ranging from 70% to 100%. In studies on sofosbuvir plus ribavirin, and sofosbuvir plus ledipasvir, the most common AEs were fatigue, insomnia, and headache. In studies on sofosbuvir in combination with Peg-IFN plus ribavirin (12 weeks) and simeprevir (12 weeks) combined with Peg-IFN plus ribavirin (24 weeks/48 weeks) response guided therapy, the most common AEs were fatigue, headache, nausea, neutropenia and anaemia. In treatment regimen with Peg-IFN plus ribavirin, more patients discontinued treatment because of AEs. In the study on daclatasvir plus sofosbuvir (12 weeks), the most frequent AEs were fatigue (17%), nausea (13%) and headache (11%) **(C0005)**.

Treatment with sofosbuvir plus ribavirin and simeprevir plus ribavirin combinations were well tolerated in the few published studies in pre- or post-liver transplant patients, with mild degrees of AEs, the most frequent being fatigue, diarrhoea, headache, and anaemia. The same was not true for OBV24 + PTV24 + RIT24 + DSV24 + RBV24 treatment. AEs were common, occurring in most (97%) patients. The most common AEs were fatigue (50%), headache (44%), cough (32%), anaemia (29%), diarrhoea (26%), and insomnia (26%), but SAEs were rare **(C0005)**.

Reimbursement

Reimbursement status of sofosbuvir; ledipasvir plus sofosbuvir, simeprevir, daclatasvir, ombitasvir plus paritaprevir plus ritonavir with or without dasabuvir is already decided or is currently in process at the national level of Member States **(A0021)**.

DISCUSSION/CONCLUSION

The introduction of well-tolerated treatment options with a high level of efficacy is welcome news for the millions of patients with chronic hepatitis C. Many patients in various stages of disease progression have been waiting for this important evolution in the management of this widespread disease.

In this health technology assessment report, the first series of such new treatment combinations are evaluated, including combinations that are IFN-free. Not surprisingly, the focus in the trials is on the SVR endpoint, an intermediate short-term outcome. This allows the companies to complete the pre-market clinical development programme in a limited number of years. Most randomised trials compared different treatment durations or the addition of ribavirin. Only very few trials compared IFN-based treatment to IFN-free combinations. This is not surprising given that the target population of IFN-free combinations is much larger than the patient group that is eligible and willing to receive IFN. Recently, in the US the Manufacturers of two first generation DAAs, telaprevir and boceprevir, voluntarily discontinued their manufacture and distribution.

Uniformly high average SVR rates greater than 90% are reported for selected DAA combinations, tailored to HCV genotype, previous treatment experience, and the absence or presence of cirrhosis, among others. The main message is that high efficacy rates combined with a very acceptable safety profile can be achieved in most subgroups defined this way.

Efficacy/Effectiveness

<u>IFN-free combinations for genotype 1</u>

Treatment-naive patients without cirrhosis, or treatment regimens containing more than one DAA (LDV/SOF12, OBV/PTV/r+DSV12+RBV12, SOF+DCV12, SOF+SMV12), have SVR12 rates above 95%. Differences exist in point estimates, but the studies do not have the power to prove that these differences are statistically different; furthermore, there are no direct comparisons between them.

In treatment-naive patients with cirrhosis, the results show a tendency towards lower SVR12 rates compared to non-cirrhotic patients, although not statistically significantly different. All

combinations have at least one study arm with a 95% CI that does not include a SVR of 75%. Some study arms have small numbers but their results do not contradict the larger study arms.

Overall, the results for treatment-experienced patients show a larger variability compared to the results for treatment naive patients. All RBV-containing combinations have at least one study arm with a lower CI that excludes 75%.

IFN-free combinations for genotypes 2, 3 and 4

For genotype 2 patients, studies on SOF+RBV show SVR12 rates ranging from 86% to 100%. In all studies but one 70% was not included in the 95% CI.

For genotype 3 patients, there is evidence only for the combinations SOF+RBV and SOF+DCV. SVR12 rates are variable, with a tendency towards better results in treatment-naive and non-cirrhotic patients, although there is no evidence that these differences are statistically significant.

For genotype 4 patients, the combination OBV/PTV/r12 excluding DSV, but with RBV, shows a SVR12 rate of 100%, with the 95% CI excluding a 90% limit. Evidence for SOF+RBV is mixed, showing a tendency towards lower SVR12 rates, with lower limits of the CI under 50%. Only one small study was found for LDV/SOF, showing a SVR12 rate of 95%, with the lower CI not including 75%.

In general, the combinations of new generation DAAs with Peg-IFN plus ribavirin are somewhat less effective compared with combinations of DAAs without Peg-IFN.

IFN-containing combinations for genotype 1

There is proof from a meta-analysis that SVR12s are superior for combinations of Peg-IFN plus ribavirin and simeprevir or sofosbuvir compared to Peg-IFN plus ribavirin alone. There are no significant differences between the new Peg-IFN plus ribavirin-based combinations. There is one study that compared Peg-IFN plus ribavirin in combination with simeprevir or telaprevir and included subgroup analysis for subtype and cirrhotic state; SVRs were found to be similar in both arms.

IFN-containing combinations for genotypes 2, 3, and 4

Results for the combinations Peg-IFN plus ribavirin with either simeprevir, sofosbuvir, or daclatasvir in genotypes 2, 3, and 4 are limited and mixed. CIs around treatment arms did not include a SVR12 lower than 50%.

Special groups

Results for HIV-positive patients and patients undergoing pre- and post-transplant are similar to those of the other patients.

Safety

A limitation of our relative safety assessment is that we used published articles of RCTs or prospective studies as a primary source for data extraction. Recent publications again stressed insufficient information from clinical trials in journal publications and results posted in clinical trial registries, however these could supplement each other to overcome the publication and outcome reporting bias. Full clinical study reports provide the most complete information on the large majority of methods and results data items; HTA doers should rely on systematic review of full clinical study reports when they become publicly available to solve the problem of overestimating benefits and underestimating harms.

Pragmatic randomised head-to-head trials or high-quality observational studies from real-world settings in larger numbers of patients will be essential for evaluating the comparative safety of the combination DAA therapies or to identify possible rare AEs. The choice of the treatment combination and duration should take into account some specific comedications and comorbidities. More studies are needed in liver transplant recipients, decompensated cirrhosis,

HIV/HCV-coinfected and renal impairment patients. None of the DAAs is free of drug interactions. Careful management of drug interactions is critical to minimise AEs in these populations.

Outcomes of relevance for the healthcare payers, including mortality and quality of life

It should be clear that the focus of the healthcare payers remains on the efficient use of treatment to reduce the burden of long-term complications associated with chronic hepatitis C. There is no direct evidence on the outcomes mortality, long-term relapses or quality of life (QoL), as studies had a short follow-up period.

Only in specific patient groups, such as patients with decompensated liver cirrhosis, publications of case series of patients treated with IFN-free combinations may provide a first indication of a reduced need for transplantation and a reduced mortality rate versus historical controls. For less advanced patients, it will take longer to observe an effect.

This can be seen as a limitation from effectiveness and especially relative effectiveness perspective. The effect of treatment on these outcomes can only be extrapolated from the indirect evidence of a residual disease progression as observed after treatments that have been on the market for a longer period, i.e. IFN-containing regimens. It is also crucial to consider that the residual disease progression after hepatitis C treatment integrates the treatment success as well as any co-factors that remain present and that continue the process towards liver cirrhosis and HCC.

Therefore, a careful evaluation of the value of SVR as an intermediate endpoint remains necessary from a healthcare payer perspective. SVR after 24 weeks of treatment is not sustained after 5 years in about 5% of cases (after Peg-INF based treatment combinations). Long term complications that are associated with chronic hepatitis C may not be caused by HCV but by confounders such as alcohol or drug abuse, and progression to certain complications e.g. the development of HCC, may continue after SVR is reached.

There is, in other words, an important degree of uncertainty about the long-term effect of treatment. So far, there are no RCTs evaluating the long-term outcomes of standard treatments based on Peg-IFN plus ribavirin versus no treatment. The two RCTs evaluating low-dose Peg-IFN versus no treatment did not show any beneficial effect of treatment, on the contrary. On a population level, no effect of treatment on survival could be detected so far. Of course, this has to do with the relatively low uptake of standard treatment in real-life practice, mainly because of the real or perceived side effects of Peg-IFN plus ribavirin combination regimen. Another factor to be considered in mortality studies in patients with chronic hepatitis C is the growing importance of PWID. Increased mortality rates that are not related to liver disease or hepatitis C are to be taken into account.

Responder analysis, although not a valid proof of treatment benefit, shows that patients with SVR fare well compared with non-responders. The residual risk of long-term complications (cirrhosis and HCC) after SVR varies between a hazard ratio of 0.62 in a large matched case-control study at the Veterans Affairs in the US to close to 0 in selected university centres in Europe. This discrepancy can, perhaps, be best explained by the presence or absence of co-factors (e.g. alcohol use, steatosis) leading to cirrhosis and HCC, independent of the presence of actively replicating HCV.

The new DAA combinations are generally well-tolerated and the treatment duration is short, often 12 weeks.

Some DAAs under assessment have different marketing authorisation status in Europe and the US.

In the US, sofosbuvir is approved for genotypes 1–4. Simeprevir was approved for genotype 1 only but now it is approved for the treatment of chronic hepatitis C virus (HCV) genotype 1 or 4 in combination with peginterferon alfa plus ribavirin, and for the treatment of HCV genotype 1 infection in adults in combination with sofosbuvir. Ledipasvir + sofosbuvir was approved in the US for genotype 1 only but now it is approved for treatment of chronic HCV genotype 1, 4, 5, or 6 infection in adults. The FDA has granted a marketing authorisation for daclatasvir for the treatment of patients with CHC genotype 3 only, in combination with sofosbuvir.

Ombitasvir + paritaprevir + ritonavir is authorised for use in the European Union (EU) under the proprietary name Viekirax. In the US, it is authorised under the proprietary name Technivie (ombitasvir + paritaprevir + ritonavir) and Viekira Pak (ombitasvir + paritaprevir + ritonavir co-packaged with dasabuvir). Viekira Pak is approved for treatment of patients with chronic HCV genotype 1 infection, including patients with cirrhosis. Viekira Pak can be used with or without ribavirin, but it is not recommended for patients with decompensated cirrhosis. Technivie is approved for use in combination with ribavirin for the treatment of HCV genotype 4 infections in patients without cirrhosis. Dasabuvir has centralized marketing authorization by the EMA for use in the EU to treat adults with HCV genotype 1.

When these new IFN-free antiviral treatments become affordable for society, the uptake of treatment is likely to increase significantly, also among patients with other co-factors of disease progression. It is therefore unlikely that the excellent long-term outcome of the patients eligible for IFN treatment and who achieved SVR can be reproduced in the broader patient population waiting for the treatment with the new combinations.

When long-term data have confirmed the safety and effectiveness, a next step to consider will be treatment as prevention of HCV transmission. A few proof-of-concept studies in PWID communities are ongoing, with first results expected within 3–4 years.

Currently, because of the high cost of the new drugs, healthcare payers restrict drug access to those in urgent need of effective treatment. Practice guidelines recommend to prioritise treatment in patients with advanced disease (e.g. Metavir fibrosis stages F3 and F4) who are at risk of developing decompensated cirrhosis and HCC in the short term. First case series published indicate that decompensation can be prevented using the new treatments, also in those patients who are not eligible for IFN-based combinations (e.g. those aged over 75 years).

However, due to the short duration of the studies and relatively small studied population the drug resistance and other efficacy measures as well as long-term safety (including oncogenic effects, an impact on overall mortality) should be monitored.

1 SCOPE

Table 1.1. Project Scope

Description	Project scope
Population	**Health conditions:** Chronic hepatitis C **International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code:** B18.2 Chronic hepatitis C **Medical Subject Headings (MeSH)-terms***: "Hepatitis C, Chronic" [*C02.440.440.120, C02.782.350.350.120, C06.552.380.350.120, C06.552.380.705.440.120] • Adults ≥ 18 years with genotype 1, 2, 3, 4, 5, and 6 chronic hepatitis C • Patients who have not been treated previously (treatment-naive) • Patients who have been treated previously (treatment-experienced) • No limitations in terms of fibrosis and/or compensated/decompensated cirrhosis and/or hepatocellular carcinoma (HCC) and/or other concomitant clinical condition(s) (see subgroup analysis section)
Interventions	**Possible new treatments (by Hepatitis C virus [HCV] genotype) and their possible comparators are listed in a separate table in the Appendix.** Local 'off-label' changes cannot be taken into account in this assessment, unless there is published high-level evidence supporting the use in clinical practice. **Sofosbuvir (SOVALDI®)** Sofosbuvir is a uridine nucleotide analogue that inhibits the HCV nonstructural protein 5B (NS5B) ribonucleic acid (RNA)-dependent RNA polymerase, preventing viral replication. Genotypes: 1 to 6. Sofosbuvir is administered orally. *Anatomical Therapeutic Chemical (ATC) code: J05AX15, MeSH term for intervention: "sofosbuvir" [C553296]* **Ledipasvir plus sofosbuvir (HARVONI®)** Sofosbuvir plus ledipasvir is a fixed-dose combination product. Sofosbuvir is a uridine nucleotide analogue that inhibits HCV NS5B RNA-dependent RNA polymerase. Ledipasvir is a macrocyclic antiviral agent and an inhibitor of the HCV NS5A protein. Both agents act to inhibit viral replication. Genotypes: 1, 3, and 4. Sofosbuvir-ledipasvir is administered orally. *ATC code: J05AX65, MeSH term for intervention: "ledipasvir, sofosbuvir drug combination" [C000595958]* **Simeprevir (OLYSIO™)** Simeprevir is a protease inhibitor. It inhibits the NS3/4A enzyme which is essential for HCV replication, thereby preventing viral replication. Used in combination with other medicines for treatment of chronic hepatitis C: pegylated interferon (Peg-IFN)-α plus ribavirin or sofosbuvir (with or without ribavirin). Genotypes: 1 and 4. Simeprevir is administered orally. *ATC code: J05AE14, MeSH term for intervention:"simeprevir" [C532453]* **Daclatasvir (DAKLINZA™)** Daclatasvir is an inhibitor of NS5A, a multifunctional phosphoprotein that plays a role in HCV replication. Used in combination with other medicines for treatment of chronic hepatitis C: sofosbuvir (with or without ribavirin) or with Peg-IFN-α and ribavirin. Genotypes: 1, 3, and 4. Daclatasvir is administered orally. *ATC code: J05AX14, MeSH-term for intervention: "BMS-790052" [C549273]* **Ombitasvir plus paritaprevir plus ritonavir (VIEKIRAX®)** Ombitasvir plus paritaprevir plus ritonavir is a fixed-dose combination product. Ombitasvir is an inhibitor of HCV NS5A, which plays a role in viral genome replication, virus assembly, and modulation of host pathways. Paritaprevir is an inhibitor of NS3/4A serine protease, which cleaves viral polyprotein after translation. Ritonavir is a cytochrome P450 (CYP) 3A4 inhibitor that increases the systemic exposure of the CYP3A4 substrate paritaprevir. Genotypes: 1 and 4. Ombitasvir + paritaprevir + ritonavir is administered orally. *ATC code: J05AX67, MeSH term for intervention: "ABT-267" (ombitasvir)*

Description	Project scope
	[C586094], "ABT-450" (paritaprevir)[C585405],"ritonavir" [D019438, D02.886.675.653, D03.383.129.708.653] **Dasabuvir (EXVIERA®)** Dasabuvir is a non-nucleoside inhibitor of HCV NS5B RNA-dependent RNA polymerase that has a role in viral genome replication, used in combination with other medicines for treatment of CHC (ombitasvir/ paritaprevir /ritonavir, with or without ribavirin). Genotype: 1. Dasabuvir is administered orally. *ATC code: J05AX16, MeSH term for intervention: "ABT-333" [C588260]*
Comparison	Active comparators include combinations based on: **Peg-IFN-α2a (PEGASYS®)/ Peg-IFN-α-2b (PEGINTRON®, VIRAFERONPEG®)** Peg-IFN-α plays a major role in the non-specific antiviral response through a variety of actions, e.g. antiviral, immunomodulatory, cytostatic, and antitumor. Peg-IFN-α is administered subcutaneously. Genotypes: 1 to 6. (ATC code: L03AB11, *MeSH term: "peginterferon alfa-2a"* [*C100416]; "peginterferon alfa-2b [C417083]")*, Peg-IFNα is often used in combination with ribavirin. **Ribavirin (REBETOL®, RIBAVIRIN MYLAN, RIBAVIRIN TEVA)** Ribavirin is a nucleoside analogue that is thought to interfere with the production or action of viral DNA and RNA. Ribavirin is used orally and in combination with other medicines for treatment of chronic hepatitis C: Peg-IFN-α-2b or IFN-α-2b (genotypes 1 to 6), or in combination with boceprevir and Peg-IFN-α-2b (genotype 1). (ATC code: J05AB04, *MeSH term: "ribavirin" [D012254]).* **Telaprevir (INCIVO®)** Telaprevir is a protease inhibitor. It inhibits the NS3/4A enzyme that is essential for HCV replication and therefore prevents viral replication. Telaprevir is administered orally, in combination with Peg-IFN-α and ribavirin (genotype 1 only). (ATC code: J05AE11, *MeSH-term: "telaprevir" [C486464])*. **Boceprevir (VICTRELIS®)** Victrelis is a protease inhibitor. It inhibits the HCV NS3 enzyme that is essential for HCV replication, thereby preventing viral replication. Victrelis is administered orally, in combination with Peg-IFN-α and ribavirin (genotype 1 only). (ATC code: J05AE12, *MeSH-term: "N-(3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl)-3-(2-((((1,1-dimethylethyl)amino)carbonyl)amino)-3,3-dimethyl-1-oxobutyl)-6,6-dimethyl-3-azabicyclo(3.1.0)hexan-2-carboxamide" [C512204])*. **See Interventions** **Rationale:** ***1.*** Comparators evaluated in clinical trials for different interventions under evaluation, (EPAR SmPC), clinical guidelines and EUnetHTA guideline on most appropriate comparator(s)[4,5] please see Appendix 1. ***2.*** The aim of the pilot is to compare new generation oral direct acting antivirals (DAAs).
Outcomes	**Efficacy outcomes:** • Sustained virological response 12 weeks after end of treatment (SVR12) • SVR 24 weeks after end of treatment (SVR24) Withdrawals before first treatment are relevant as these may be higher if randomised to IFN-containing arm in open-label RCTs • Development of resistance (and transmission of resistant strains) • Relapse rate after SVR12/24 • Progression of liver fibrosis • Incidence of decompensated liver disease and HCC (and the associated need for liver transplantation) • Health-related quality of life (HRQoL)

Description	Project scope
	• Mortality **Safety Outcomes:** • Adverse events (AEs) of treatment (any AEs, discontinuation due to AE, serious AEs (SAEs), Death as SAE, most frequent AE) Drug–drug interactions will be discussed if they result in AEs. Rationale for choosing the outcomes: commonly used outcomes in clinical studies on hepatitis C, clinical guidelines, and outcomes important for REA; based on recommendations from the EUnetHTA methods Guideline on Clinical and Surrogate Endpoints and Safety[6-8].
Subgroups analysis **(If possible with available data)**	• Treatment naive or non-responder to previous treatment • Baseline fibrosis stage (i.e. presence or absence of cirrhosis) • Baseline HCV RNA • Presence or absence of HIV-coinfection • Presence or absence of HBV-coinfection • Patients intolerant to or ineligible for IFN treatment • Patients treated pre- and post-liver transplantation • Presence or absence of Interleukin (IL)-28b polymorphism (in IFN-based regimens) • Presence or absence of baseline resistance (NS5A, NS3) • HCV subtypes (1a, 1b, etc.)
Study design	• RCTs • Prospective observational studies • Prospective uncontrolled trials

2 METHODS AND EVIDENCE INCLUDED

2.1. Pilot team

The work was distributed as follows.

Table 2.1. Pilot Team

Name/Institution	Country	Role
A. Gemelli	Italy	Author of Health Domain
AAZ	Croatia	Author Safety and Technology Domains
KCE	Belgium	Author Effectiveness Domain
HVB	Austria	Co-Author Overall support

2.2. Search

A systematic literature search (not limited by publication date) was performed according to EUnetHTA guidance on information retrieval.

A health information expert developed a search strategy that was first reviewed and discussed with two experts.

The following databases were searched: MEDLINE (accessed through OVID); EMBASE; and the Cochrane Library databases: The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews (Cochrane Reviews), The Database of Abstracts of Reviews of Effects (DARE), and The Health Technology Assessment Database (HTA).

An initial search was carried out in May 2015, and an updated search performed 4 months later, in September 2015. Details of the search strategy are provided in Appendix 1, including exact search dates per database. In summary, the search was carried out on MeSH terms and keywords. The main terms used were antiviral agents, antiviral, sofosbuvir, sovaldi, "interferon-sparing", HCV polymerase inhibitors, abt 267, interferon-free, abt 450, abt 333, ombitasvir, paritaprevir, ritonavir, dasabuvir, simeprevir, daclatasvir, and BMS-790052.

In addition, the following clinical trials registries were assessed, for registered completed, ongoing and withdrawn clinical trials or results posted through the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). The search strategy is detailed in the Appendix 1.

The marketing authorisation holders were asked to submit reports, however, only one company, Johnson & Johnson did so. We included data provided by that report where no full-text publication published in a peer-reviewed journal was available. Input was also provided by market authorisation holders during the public consultation phase.

Relevant references identified using the literature search were collated in one Endnote file and duplicates were removed. References in the Endnote file were screened and assessed for eligibility independently by two reviewers. The reference lists of relevant systematic reviews and HTA reports were checked for other relevant studies.

Differences in selection results were discussed in order to achieve consensus; a third reviewer was consulted in case of uncertainty. The study selection process is presented below.

The study types included in the clinical effectiveness and safety domains focused on RCTs and prospective uncontrolled trials. In addition, for combinations with peg-IFN and ribavirin we decided to update a recently published systematic review of high quality. We only looked for HTA reports and systematic reviews published in 2014 or 2015 and with a search date not older than 2014, as the usefulness of older systematic reviews is limited. We selected one systematic review published by CADTH in October 2014 and assessed the quality using AMSTAR.

Inclusion/exclusion criteria:

- RCTs, prospective uncontrolled trials, prospective observational studies.
- At least one study arm containing a drug combination from our list of interventions, and administered according to EPAR.
- Available in full text, or with additional information from the marketing authorisation holder.
- Studies were not selected on outcome. No language restrictions were applied.
- Studies available only in abstract, editorial, or review format did not meet the inclusion criteria.

Figure 2.1. shows the flow chart for the study selection. In total, 49 studies were retained for assessment. Evidence tables can be found in the Appendix 1.

Eight studies (reported in seven publications) were excluded after examining the full text

- Kowdley[9]. Exploratory dose- and duration-finding study comparing 14 different regimens; SVR 24 only reported, but not in detail.
- Poordad[5]. Exploratory study that investigated only paritaprevir, and not ombitasvir, in combination with dasabuvir – a combination that is not recognised by the EMA.
- Lawitz[10]. None of the study arms contained a regimen approved by the EMA-for HCV genotypes 1–3. Regimens without dasabuvir are recognised only for genotype 4.
- CONCERTO 1–4 and DRAGON studies. The dose of simeprevir investigated was lower than that recommended in the EPAR[7,8,11,12].

The same was not true for Safety Domain: to answer specific assessment element questions in Safety Domain Lawitz[10] LONESTAR study and five studies (in 4 publications[7,8,11,12]) on interferon-containing regimens for genotype 1 HCV infection were used.

A list of planned and ongoing studies is provided in the Appendix 1.

For the Peg-IFN plus ribavirin-containing regimens, we updated a systematic review published by CADTH[13]. Amstar scores were:

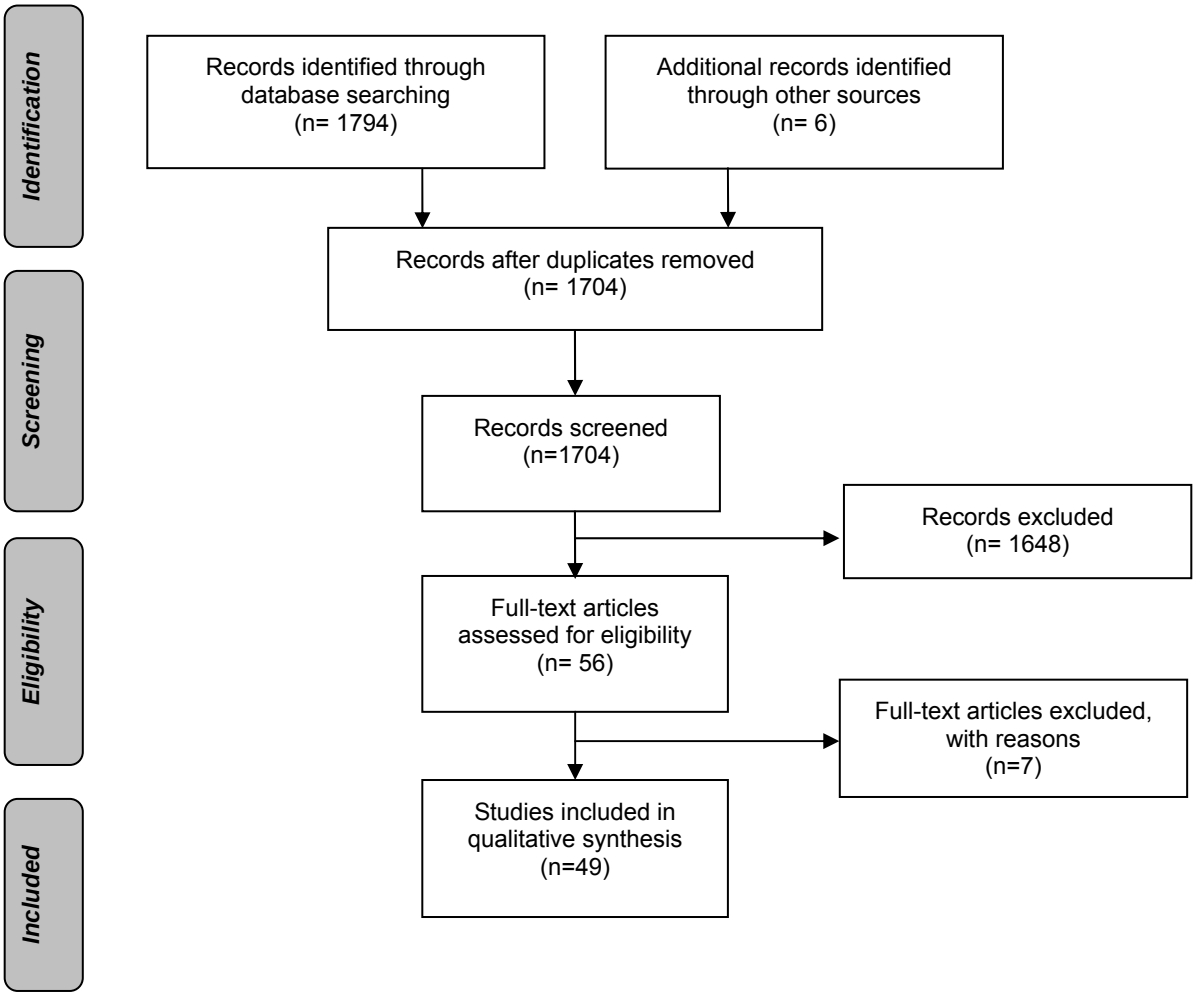
Table 2.3. AMSTAR scores for the updated SR on Peg-IFN plus ribavirin-containing regimens

1. Did it have an 'a priori' design?	Yes	
2. Was there duplicate study selection and data extraction?	Yes	

3. Was a comprehensive literature search performed?	Yes	MEDLINE (1946–) with In-Process records and daily updates through Ovid; Embase (1974–) through Ovid; the Cochrane Central Register of Controlled Trials through Ovid; and PubMed.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes	
5. Was a list of studies (included and excluded) provided?	Yes	
6. Were the characteristics of the included studies provided?	Yes	
7. Was the scientific quality of the included studies assessed and documented?	Yes	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	
9. Were the methods used to combine the findings of studies appropriate?	Yes	Network meta-analysis and direct comparisons, proper evaluation of heterogeneity
10. Was the likelihood of publication bias assessed?	Not applicable	Too few studies per category to use funnel plot or statistical analysis
11. Was the conflict of interest included?	No	

2.3. Flow chart of study selection

Figure 2.1. Flow chart



2.4. Quality rating of studies

We used the Cochrane Collaboration risk of bias concept to assess the internal validity of RCTs within a REA. We used the guidance provided in Chapter 8 and Table 8.5.d of the Cochrane Handbook[14] as recommended by the EUnetHTA guidance[15]. However, the nature of the available evidence forced us to make some modifications. Studies were either single-arm studies, or RCTs where the randomisation was not relevant to our research question (i.e. the same regimen was randomised with or without ribavirin and, in some cases, for varying treatment durations). Therefore, we determined that allocation concealment and random sequence generation were non-applicable in these cases. We did not use assessment tools for observational studies as the tools recommended in the guidance were designed for comparative studies and focused on comparability of comparison groups and confounding, which is in not relevant in observational studies. Risk of bias was evaluated independently by two reviewers.

2.5. Data extraction

Data extraction was performed by one reviewer on pre-defined extraction tables and double-checked regarding completeness and accuracy by a second reviewer. Differences in extraction results were discussed to achieve consensus; a third reviewer was involved in case of uncertainty. Detailed data extraction tables are included in Appendix 1.

2.6. Analyses and pooling

When the primary studies were assessed and summarised, the possibilities to combine the studies using direct (meta-analysis) and indirect comparison methods, including network meta-analysis, were considered. Apart from some combinations with IFN, that were compared to Peg-IFN plus ribavirin alone, studies did not use a comparison group, or only compared combinations with and without ribavirin and with different treatment durations, and were de facto single-arm studies. Therefore, neither a 'classic' nor a 'network' meta-analysis was possible. This will be further justified in the results and discussion sections.

GRADE

We planned to assess direct evidence related to efficacy and safety using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE)-methodology (a summary of this approach can be found in Appendix 4). However, given that the bulk of the evidence consisted of non-comparative studies, the GRADE approach becomes problematic as there are no effect measures available. The GRADE approach does not provide guidance in such circumstances. Therefore, the results will be considered by GRADE automatically and uniformly as a very low level of evidence, thus limiting the usefulness of the approach.

2.7. Deviations from project plan

We used one high quality systematic review for the IFN-containing regimens that was part of a recent HTA report. For the more recent IFN-free combinations, evidence was too recent to be captured by a systematic review and therefore it was not efficient to initiate a search and assess systematic reviews on this topic. The evidence did not allow us to pool studies nor to conduct a network meta-analysis; reasons for this will be discussed in the results section. We had to adapt the evaluation tools, as explained in section 2.4. We searched for RCTs, and prospective uncontrolled trials and prospective observational studies, but not for retrospective studies.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE TECHNOLOGY

3.1. Research questions

Element ID	Research question
B0001	What are sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators?
A0020	For which indications have sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators received marketing authorisation?
B0002	What is the claimed benefit of sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir and dasabuvir in relation to the comparators and one in comparison to each other?
B0004	Who administers sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed for sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators?
A0021	What is the reimbursement status of sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir and dasabuvir?

3.2. Results

Features of the technology and comparators

[B0001] What are sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators?

As described in the project plan for this assessment, we primarily focused on the assessment of recently authorised direct-acting antivirals (DAAs) (nucleoside non-structural [NS] 5B polymerase inhibitors, NS5A inhibitors, NS3-4A protease inhibitors, non-nucleoside NS5B polymerase inhibitors): sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir with or without dasabuvir and/or combinations of these products in an IFN-free regimen or IFN-containing regimen (Table 3.1.).
These new treatment options are compared with the options that have been on the market for longer (peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, telaprevir, boceprevir) (Table 3.2.) and also compared with each other.

Table 3.1. Features of the technologies (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir with or without dasabuvir)

Interventions	sofosbuvir	ledipasvir + sofosbuvir	simeprevir	daclatasvir	ombitasvir + paritaprevir + ritonavir	dasabuvir
Proprietary name	Sovaldi	Harvoni	Olysio	Daklinza	Viekirax (EU); Technivie (US); Viekira Pak* (US)	Exviera (EU); Viekira Pak* (US)
Active substance	sofosbuvir	ledipasvir + sofosbuvir	simeprevir	daclatasvir dihydro-chloride	ombitasvir + paritaprevir + ritonavir	dasabuvir sodium
Pharmaceutical form, Quantitative composition, Route of administration	400 mg film-coated tablets (for oral use)	90 mg/400 mg film-coated tablets (for oral use)	150 mg hard capsules (for oral use)	30 mg or 60 mg film-coated tablets (for oral use)	12.5 mg/75 mg/50 mg film-coated tablets (for oral use)	250 mg film-coated tablets (for oral use)
ATC code	J05AX15	J05AX65	J05AE14	J05AX14	J05AX67	J05AX16

In US: Viekira Pak (ombitasvir/paritaprevir/ritonavir co-packaged with dasabuvir)
Abbreviations: ATC=Anatomical Therapeutic Chemical; EMA=European Medicines Agency; FDA=Food and Drug Administration
Sources: SmPC (EMA)[16-21]; FDA[22]

Table 3.2. Features of the comparators (peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, telaprevir, boceprevir)

Comparators	peginterferon alfa-2a	peginterferon alfa-2b	ribavirin	telaprevir	boceprevir
Proprietary name	Pegasys	PegIntron; ViraferonPeg (EU)	Rebetol; Generics: Ribavirin Mylan Ribavirin Teva, Ribavirin Teva Pharma B.V.	INCIVO (EU); Incivek (US)	Victrelis
Active substance	peginterferon alfa-2a	peginterferon alfa-2b	ribavirin	telaprevir	boceprevir
Pharmaceutical form, Quantitative composition, Route of administration	135 µg or 180 µg solution for injection (subcutaneous use) 90 µg or 135 µg or 180 µg solution for injection in	50 µg or 80 µg or 100 µg or 120 µg or 150 µg powder and solvent for solution for injection (subcutaneous use)	200 mg or 400 mg film-coated tablets (for oral use)	375 mg film-coated tablets (for oral use)	200 mg hard capsules (for oral use)

Comparators	peginterferon alfa-2a	peginterferon alfa-2b	ribavirin	telaprevir	boceprevir
	pre-filled syringe (subcutaneous use) 135 µg or 180 µg solution for injection in pre-filled pen (subcutaneous use)	50 µg or 80 µg or 100 µg or 120 µg or 150 µg powder and solvent for solution for injection in pre-filled pen (subcutaneous use)			
ATC code	L03AB11	L03AB10	J05AB04	J05AE11	J05AE12

Abbreviations: ATC=Anatomical Therapeutic Chemical; EMA=European Medicines Agency; FDA=Food and Drug Administration
Sources: SmPC (EMA)[23-27]; FDA[22]

Technologies under assessment (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir with or without dasabuvir)

Sofosbuvir

Sofosbuvir is a pan-genotypic inhibitor of the hepatitis C virus (HCV) NS5B ribonucleic acid (RNA)-dependent RNA polymerase, the enzyme essential for viral replication of the hepatitis C virus. It is active against all six HCV genotypes.

Sofosbuvir acts as a nucleotide prodrug, which delivers the monophosphorylated uridine nucleotide into human hepatocytes. Two additional phosphate groups are added by intracellular enzymes and sofosbuvir is converted to the uridine nucleoside analog triphosphate GS-461203. Pharmacologically active GS-461203 competes with endogenous uridine triphosphate for incorporation into the growing HCV RNA chain during the replication process carried out by NS5B RNA-dependent RNA polymerase enzyme. Once incorporated, no further nucleotides can be added and the RNA chain is terminated.

Sofosbuvir is indicated in combination with other medicinal products, such as ribavirin or a combination of peginterferon alfa and ribavirin, for the treatment of chronic hepatitis C (CHC) in adults.

Contraindications and special warnings and precautions for use are listed in Table 3.3.

Further details on administration and dosing, according to the European Medicines Agency (EMA, may be found in Appendix 1).

Table 3.3. Summary data on sofosbuvir, according to the European Medicines Agency (EMA)

Sofosbuvir (Sovaldi)	
Active substance	sofosbuvir
ATC code	DAA; ATC code: J05AX15
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substance or to any of the excipients in sofosbuvir.
SAEs	Cases of severe bradycardia and heart block have been observed when sofosbuvir is used in combination with daclatasvir and concomitant amiodarone

Sofosbuvir (Sovaldi)	
	and/or other drugs that lower heart rate.
Special warnings and precautions for use	Not recommended for administration as monotherapy; treatment-experienced patients with genotype 1, 4, 5, and 6 HCV infection (no optimal treatment duration established); treatment of patients with genotype 5 or 6 HCV infection (limited data); IFN-free therapy for genotype 1, 4, 5, and 6 HCV infection (optimal regimen and treatment duration have not been established); co-administration with other DAAs against HCV (telaprevir, boceprevir); pregnancy and concomitant use with ribavirin; use with potent P-gp inducers; renal impairment; HCV/HBV co-infection; paediatric population. Cases of severe bradycardia and heart block have been observed when sofosbuvir is used in combination with daclatasvir and concomitant amiodarone and/or other drugs that lower heart rate.
Adult dosing	One 400 mg tablet, taken orally, once daily with food. Sofosbuvir should be used in combination with other medicinal products. Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with sofosbuvir. The dose of ribavirin, when used in combination with sofosbuvir, is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg) and administered orally in two divided doses with food.
Recommended duration of treatment	12–24 weeks; dependent on viral genotype and patient population. Patient with CHC awaiting liver transplantation – until liver transplantation.

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; DAA=direct-acting antiviral; EMA=European Medicines Agency; HBV= hepatitis B virus; IFN=interferon; P-gp=P-glycoprotein; SAE=serious adverse event
Source: SmPC (EMA), last update 21/09/2015 [16]

Serious adverse effects listed in Micromedex are hematologic: pancytopenia (les than 1%); hepatic: increased bilirubin level (1%-3%) and psychiatric: severe depression (less than 1%), suicidal thoughts, suicide[3].

The EMA recommends avoidance of certain hepatitis C medicines and amiodarone together because concomitant use may increase risk of slow heart rate and related problems. EMA has confirmed a risk of severe bradycardia or heart block when the hepatitis C medicines sofosbuvir+ledipasvir or a combination of sofosbuvir and daclatasvir are used in patients who are also taking the medicine amiodarone[28].

Ledipasvir + sofosbuvir

Ledipasvir + sofosbuvir are active substances of Harvoni. Both sofosbuvir as well as ledipasvir are DAAs used for HCV treatment with very high efficacy against genotypes 1, 3, and 4.

Sofosbuvir is a nucleotide prodrug, pan-genotypic inhibitor of HCV NS5B RNA-dependent RNA polymerase. Extensively metabolised in the human hepatocyte, sofosbuvir is transformed into active uridine triphosphate analogue (GS-461203), which competes with endogenous uridine triphosphate for incorporation into nascent viral RNA chains by the NS5B polymerase and acts as a chain terminator.

The mechanism of action of ledipasvir has not been determined in detail, but indirect evidence exists of HCV NS5A protein being its target. Protein NS5A, essential for both RNA replication and the assembly of HCV virions, has no enzymatic function, so no biochemical assay can be performed at this time to directly confirm NS5A inhibition by ledipasvir. *In vitro* resistance selection and cross-resistance studies, and the lack of HCV enzyme or kinase inhibition, was taken to support the conclusion that ledipasvir targets NS5A as its mode of action.

Contraindications and special warnings and precautions for use are listed in Table 3.4.

Further details on administration and dosing, according to the EMA, may be found in Appendix 1.

Table 3.4. Summary data on ledipasvir + sofosbuvir, according to EMA

Ledipasvir + sofosbuvir (Harvoni)	
Active substance	ledipasvir + sofosbuvir
ATC code	DAA, ATC code: not yet assigned
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substances or to any of the excipients in ledipasvir or sofosbuvir. Co-administration with rosuvastatin or St. John's wort (*Hypericum perforatum*).
SAEs	Cases of severe bradycardia and heart block have been observed when it is used with concomitant amiodarone and/or other drugs that lower heart rate.
Special warnings and precautions for use	Should not be administered concomitantly with other medicinal products containing sofosbuvir; limitations for genotype-specific activity (limited clinical data on use in patients infected with HCV genotype 3 and 4; efficacy of ledipasvir/sofosbuvir has not been studied against HCV genotype 2, 5, and 6); treatment of patients with prior exposure to HCV DAAs; renal impairment; patients with decompensated cirrhosis and/or who are awaiting liver transplant or post-liver transplant; potent P-gp inducers significantly decrease ledipasvir and sofosbuvir plasma concentration; use with certain HIV antiretroviral regimens; use with HMG-CoA reductase inhibitors - it can significantly increase the concentration of the statin; HCV/HBV co-infection; paediatric population-not recommended under 18 yrs; excipients: colouring agent sunset yellow FCF aluminium lake (E110)- – may cause allergic reactions and lactose -– not use in galactose intolerance..
Adult dosing	One tablet once daily with or without food. Each film-coated tablet contains 90 mg ledipasvir and 400 mg sofosbuvir. When used in combination with ribavirin, refer also to the Summary of Product Characteristics of ribavirin. In patients without decompensated cirrhosis requiring the addition of ribavirin to their treatment regimen, the daily dose of ribavirin is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg) and administered orally in two divided doses with food.
Recommended duration of treatment	12–24 weeks, depending on patient population and viral genotype (8 weeks may be considered in naive genotype 1- infected patients).

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; DAA=direct-acting antiviral; EMA=European Medicines Agency; HBV=hepatitis B virus; SAE=serious adverse event
Source: SmPC (EMA), last update 24/07/2015 [17]

Serious adverse effects listed in Micromedex are psychiatric: suicidal behaviour (less than 1% with sofosbuvir plus ribavirin or pegylated interferon/ribavirin) and suicidal thoughts (less than 1% with sofosbuvir plus ribavirin or pegylated interferon/ribavirin)[3].

Postmarketing data: Skin rashes, sometimes with blisters or angioedema-like swelling, has been reported[3].

Recommendations released by EMA (avoidance of certain hepatitis C medicines and amiodarone together due increased risk of slow heart rate and related problems) could be seen above, in data written on sofosbuvir.

Simeprevir

Simeprevir is a specific inhibitor of HCV NS3-4A serine protease.

The NS3-4A serine protease is a heterodimer complex formed by two non-covalently bound HCV-encoded proteins: a catalytic subunit (the N-terminal serine protease domain of NS3) and activation subunit (the NS4A cofactor). This enzyme is responsible for the proteolytic cleavage of the HCV polyprotein precursor at four different positions. Inhibition of NS3-4A serine protease prevents HCV from completing its life cycle. Simeprevir is extensively metabolised in the liver. The hepatic CYP3A4 system is responsible for the majority of simeprevir oxidative metabolism; possible involvement of CYP2C8 and CYP2C19 systems in the process cannot be excluded.

Once administered, simeprevir is found to be extensively bound to plasma proteins (>99.9%), primarily to albumin and, to a lesser extent, alfa-1-acid glycoprotein.

Simeprevir must not be administered as monotherapy. Recommended medicinal products for co-administration with simeprevir for the treatment of CHC are peginterferon alfa + ribavirin or sofosbuvir (± ribavirin).

Both simeprevir + peginterferon alfa + ribavirin combination treatment and simeprevir + sofosbuvir (with or without ribavirin) combination treatment showed similar safety findings.

Contraindications and special warnings and precautions for use are listed in Table 3.5.

Further details on administration and dosing, according to the EMA, may be found in Appendix 1.

Table 3.5. Summary data on simeprevir, according to EMA

Simeprevir (Olysio)	
Active substance	simeprevir
ATC code	Antiviral for systemic use, DAA; ATC code: J05AE14
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substance or to any of the excipients in simeprevir.
SAEs	Reported in 0.3% of simeprevir + peginterferon alfa + ribavirin treated patients; photosensitivity events requiring hospitalisation.
Special warnings and precautions for use	Should not be used in treatment of patients with HCV genotypes 2, 3, 5, or 6; must not be administered as monotherapy; use of simeprevir in patients infected with HCV genotype 1a (with the NS3 Q80K polymorphism)-)- simeprevir efficacy in combination with peginterferon alfa and ribavirin is substantially reduced; IFN-free therapy optimal regimen and treatment duration for interferon-free regimens have not yet been established; co-administration with other DAAs against HCV - HCVif the benefits are considered to outweigh the risks based upon available data. There are no data to support the co-administration of simeprevir and telaprevir or boceprevir. These HCV protease inhibitors are anticipated to be cross-resistant, and co-administration is not recommended; simeprevir in combination with peginterferon alfa-2b--patient obtained numerically lower SVR12 rates and also experienced viral breakthrough and viral relapse more frequently than those treated with simeprevir in combination with peginterferon alfa-2a and ribavirin; pregnancy and contraception- – use only if the benefit justifies the risk. Female patients of childbearing potential must use an effective form of contraception; photosensitivity; rash; hepatic impairment-- simeprevir plasma exposure is significantly increased in subjects with severe hepatic impairment; laboratory testing during treatment with simeprevir, peginterferon alfa and ribavirin (HCV RNA levels should be monitored at weeks 4 and 12); interactions with medicinal products (co-administration with substances that moderately or strongly induce or inhibit cytochrome P450 3A (CYP3A4) is not recommended); HBV co-infection; organ transplant patients- co-administration with ciclosporin is not recommended as this leads to significantly higher exposure of simeprevir; contains lactose monohydrate monohydrate – not use in galactose intolerance.

Simeprevir (Olysio)	
	Cases of bradycardia have been observed when it is used in combination with sofosbuvir and concomitant amiodarone.
Adult dosing	One capsule of 150 mg once daily for 12 weeks, taken with food. Simeprevir must not be administered as monotherapy. Simeprevir must be used in combination with other medicinal products for the treatment of CHC. When considering simeprevir combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, patients should be tested for the presence of virus with the NS3 Q80K polymorphism before starting treatment. Refer also to the Summary of Product Characteristics of the medicinal products that are used in combination with simeprevir.
Recommended duration of treatment	12/24/48 weeks depending on cirrhosis, HIV co-infection, response on therapy

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; DAA=direct-acting antiviral; EMA=European Medicines Agency; HBV=hepatitis B virus; IFN=interferon; SAE=serious adverse event
Source: SmPC (EMA), last update 25/09/2015 [18]

Serious adverse effects listed in Micromedex are dermatologic: photosensitivity (5%-7%), rash (grade 3, 1%); hepatic: liver failure[3].

Postmarketing data: cases of hepatic decompensation and hepatic failure, including fatal cases have been reported during treatments with simeprevir in combination with peginterferon alfa and ribavirin or in combination with sofosbuvir. Most cases were reported in patients with advanced and/or decompensated cirrhosis who are at increased risk for hepatic decompensation or hepatic failure[29].

Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is co-administered with sofosbuvir in combination with another HCV direct acting antiviral, including simeprevir[29].

Daclatasvir

Daclatasvir is a first in class DAA agent. Daclatasvir acts as an NS5A inhibitor. Protein NS5A is a multifunctional protein, which is an essential component of HCV replicase; it has the ability to modulate the host cell IFN response and is clearly involved in both viral RNA replication and virus particle assembly. Daclatasvir, therefore, inhibits both viral RNA replication and virion assembly.

Daclatasvir must be administered in combination with other medicinal products for CHC infection; monotherapy is not indicated. Combination therapies include daclatasvir co-administered with sofosbuvir (with or without ribavirin) or daclatasvir administered in combination with peginterferon alfa and ribavirin.

Contraindications and special warnings and precautions for use are listed in Table 3.6. Details should be found in SmPC (EMA).

Further details on administration and dosing, according to the EMA, may be found in Appendix 1.

Table 3.6. Summary data on daclatasvir, according to EMA

Daclatasvir (Daklinza)	
Active substance	daclatasvir dihydrochloride
ATC code	DAA; ATC code: J05AX14
Approved indication in the treatment of chronic hepatitis C virus (HCV) infection in adults	Yes (in EU); Yes in US, but only for genotype 3 in combination with sofosbuvir[3].

Daclatasvir (Daklinza)	
Contraindications	Hypersensitivity to the active substance or to any of the excipients in daclatasvir. Co-administration with strong inducers of CYP3A4 and P-gp (e.g., phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, rifapentine, systemic dexamethasone, the herbal product St John's wort *(Hypericum perforatum)*).
SAEs	Cases of severe bradycardia and heart block have been observed when daclatasvir is used in combination with sofosbuvir and concomitant amiodarone and/or other drugs that lower heart rate
Special warnings and precautions for use	Must not be administered as monotherapy; the combinations of daclatasvir and sofosbuvir have been evaluated in a limited number of patients with cirrhosis; severe bradycardia and heart block (have been observed when daclatasvir is used in combination with sofosbuvir and concomitant amiodarone with or without other drugs that lower heart rate, the mechanism is not established, cases are potentially life threatening, therefore amiodarone should only be used in patients on daclatasvir and sofosbuvir when other alternative antiarrhythmic treatments are not tolerated or are contraindicated); for genotype-specific activity; decompensated liver disease; in case of retreatment with daclatasvir; pregnancy and contraception requirements; organ transplant; HCV/human immunodeficiency virus (HIV) co-infection; HCV/HBV co-infection; in elderly patients; in paediatric population; possible interactions with other medicinal products; contains lactose.
Adult dosing	The recommended dose of daclatasvir is 60 mg once daily, to be taken orally with or without meals. Daclatasvir must be administered in combination with other medicinal products. The dose of ribavirin, when combined with daclatasvir, is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg).
Recommended duration of treatment	12–24 weeks

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; DAA=direct-acting antiviral; EMA=European Medicines Agency; HBV=hepatitis B virus; HIV=human immunodeficiency virus; SAE=serious adverse event
Source: SmPC (EMA), last update 05/11/2015[19]

EMA recommends avoidance of certain hepatitis C medicines and amiodarone together because concomitant use may increase risk of slow heart rate and related problems. EMA has confirmed a risk of severe bradycardia or heart block when the hepatitis C medicines sofosbuvir+ledipasvir or a combination of sofosbuvir and daclatasvir are used in patients who are also taking the medicine amiodarone[28].

Ombitasvir + paritaprevir + ritonavir

Ombitasvir, paritaprevir and ritonavir are active substances of ombitasvir + paritaprevir + ritonavir (Table 3.7.). This fixed combination of three different DAA agents, with three different modes of action and non-overlapping resistance profiles, enables targeting HCV at multiple steps in its viral life cycle.

Ombitasvir is an inhibitor of HCV NS5A, a non-structural HCV protein. Protein NS5A has no known direct enzymatic function but is an essential component of HCV replicase and, therefore, essential for viral replication. NS5A has the ability to modulate the host cell interferon response and clearly plays multiple roles in mediating viral replication, host–cell interactions, and viral pathogenesis.

Paritaprevir is an inhibitor of HCV NS3-4A protease. The NS3-4A serine protease is a heterodimer complex formed by two non-covalently bound HCV-encoded proteins: a catalytic subunit (the N-terminal serine protease domain of NS3) and activation subunit (the NS4A cofactor). This serine protease is necessary for the proteolytic cleavage of the HCV-encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. Ritonavir does not act against HCV directly. It is a potent cytochrome P450 3A4 inhibitor used as a pharmacokinetic enhancer. Ritonavir is a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir.

Ombitasvir + paritaprevir + ritonavir are administered in combination with dasabuvir or ribavirin or in combination with both dasabuvir and ribavirin depending on genotype and presence or absence of cirrhosis.

Further details on administration and dosing, according to EMA, may be found in Appendix 1.

Table 3.7. Summary data on ombitasvir + paritaprevir + ritonavir, according to EMA

Ombitasvir + paritaprevir + ritonavir (Viekirax)	
Active substance	ombitasvir + paritaprevir + ritonavir
ATC code	Antivirals for systemic use; DAAs; ATC code: J05AX67
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substances or to any of the excipients of ombitasvir, paritaprevir, or ritonavir. Patients with severe hepatic impairment (Child-Pugh C). Use of ethinyloestradiol-containing medicinal products such as those contained in most combined oral contraceptives or contraceptive vaginal rings. Medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events must not be co-administered with ombitasvir + paritaprevir + ritonavir. Examples of CYP3A4 substrates include: alfuzosin hydrochloride; amiodarone, astemizole, terfenadine, cisapride, colchicine in patients with renal or hepatic impairment, ergotamine, dihydroergotamine, ergonovine, methylergometrine, fusidic acid, lovastatin, simvastatin, atorvastatin, oral midazolam, triazolam, pimozide, quetiapine, quinidine, salmeterol, sildenafil (when used for the treatment of pulmonary arterial hypertension), ticagrelor. Co-administration of ombitasvir + paritaprevir + ritonavir with or without dasabuvir with medicinal products that are strong or moderate enzyme inducers is expected to decrease ombitasvir, paritaprevir, and ritonavir plasma concentrations and reduce their therapeutic effect and must not be co-administered. Examples of enzyme inducers include: carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine, etravirine, enzalutamide, mitotane, rifampicin, St. John's Wort (*Hypericum perforatum*). Co-administration of ombitasvir + paritaprevir + ritonavir with or without dasabuvir with medicinal products that are strong inhibitors of CYP3A4 is expected to increase paritaprevir plasma concentrations and must not be co-administered with ombitasvir + paritaprevir + ritonavir. Examples of CYP3A4 inhibitors include: cobicistat, indinavir, lopinavir/ritonavir, saquinavir, tipranavir, itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, conivaptan.

Ombitasvir + paritaprevir + ritonavir (Viekirax)	
SAEs	serum ALT elevations, serum bilirubin elevations
Special warnings and precautions for use	Not recommended for administration as monotherapy; must be used in combination with other medicinal products for the treatment of HCV. Genotype-specific activity (the efficacy has not been established for HCV genotypes 2, 3, 5 and 6 and, therefore, ombitasvir + paritaprevir + ritonavir should not be used to treat patients infected with these genotypes; no data are available on the use of ombitasvir + paritaprevir + ritonavir and ribavirin in patients with HCV genotype 4 infection with compensated cirrhosis and, therefore, the optimal treatment duration has not been established; based on *in vitro* antiviral activity and available clinical data on HCV genotype 1, a conservative treatment duration of 24 weeks is recommended for patients with HCV genotype 4 and compensated cirrhosis). Co-administration with other DAAs against HCV (other than dasabuvir and/or ribavirin). Retreatment; pregnancy and concomitant use with ribavirin; alanine aminotransferase (ALT) elevations; use with glucocorticoids metabolised by CYP3A (e.g., fluticasone); use with colchicine; use with statins (contraindicated: simvastatin, lovastatin and atorvastatin; use with caution: rosuvastatin, pitavastatin and fluvastatin); treatment of patients with HIV co-infection; hepatic impairment; HCV/HBV co-infection; paediatric population.
Adult dosing	The recommended oral dose is two 12.5 mg / 75 mg / 50 mg tablets once daily (in the morning) with food. Ombitasvir + paritaprevir + ritonavir should be used in combination with other medicinal products for the treatment of HCV.
Recommended duration of treatment	12–24 weeks, depending on patient population and HCV genotype

Abbreviations: ALT=alanine aminotransferase; ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; DAA=direct-acting antiviral; EMA=European Medicines Agency; SAE=serious adverse event
Source: SmPC (EMA), last update 28/09/2015[20]

Serious adverse effects listed in Micromedex are ALT level increase (1%) and injury of liver. Postmarketing data showed cases of hepatic decompensation and hepatic failure reported during postmarketing treatments (Viekira Pak and Technivie) suggested a potential causal association with starting treatment and resolution of symptoms in some patients after the treatment was stopped[3,30].

Dasabuvir

Dasabuvir is a non-nucleoside, viral polymerase inhibitor that blocks the replication of the HCV genome (Table 3.8. and Table 3.9.).

Dasabuvir inhibits HCV RNA-dependent RNA polymerase, the enzyme encoded by the NS5B gene. When used in combination with other medicines (ombitasvir/paritaprevir/ritonavir, with or without ribavirin), dasabuvir is effective treatment against genotypes 1a and 1b of HCV. Co-administration of dasabuvir with ombitasvir/paritaprevir/ritonavir combines three DAA agents with distinct mechanisms of action and non-overlapping resistance profiles. This strategy enables targeting of HCV at multiple stages in the viral life cycle. Dasabuvir is administered in combination with ombitasvir + paritaprevir + ritonavir.

Dasabuvir is mainly metabolised by CYP2C8 enzyme and to a lesser extent by CYP3A enzyme. Seven dasabuvir metabolites were identified in plasma. The most abundant plasma metabolite detected was M1, which represented 21% of all dasabuvir-related metabolites formed via oxidative metabolism, predominantly by CYP2C8.

Further details on administration and dosing, according to EMA may be found in Appendix 1.

Table 3.8. Summary data on dasabuvir, according to EMA

Dasabuvir (Exviera)	
Active substance	dasabuvir sodium
ATC code	Antiviral for systemic use; DAA; ATC code: J05AX16
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substances or to any of the excipients in dasabuvir; use of ethinyloestradiol-containing medicinal products (e.g., those contained in most combined oral contraceptives or contraceptive vaginal rings); co-administration of dasabuvir with medicinal products that are strong or moderate enzyme inducers is expected to decrease dasabuvir plasma concentrations and reduce its therapeutic effect (e.g., carbamazepine, phenytoin, phenobarbital; efavirenz, nevirapine, etravirine; enzalutamide; mitotane; rifampicin; St. John's Wort (*Hypericum perforatum*)); co-administration of dasabuvir with medicinal products that are strong CYP2C8 inhibitors may increase dasabuvir plasma concentrations (e.g., gemfibrozil); contraindications related to ombitasvir/paritaprevir/ritonavir treatment (dasabuvir is administered with ombitasvir/paritaprevir/ritonavir).
SAEs	Grade 3-4 Hb level↓; ALT and total bilurubin↑.
Special warnings and precautions for use	For different genotype-specific activity (recommended use only in patients with HCV genotype 1); not recommended for use as monotherapy; co-administration with other DAAs against HCV (with the exception of treatment combination with ombitasvir/paritaprevir/ritonavir with or without ribavirin); retreatment; pregnancy and concomitant use with ribavirin; ALT elevations; use with statins (rosuvastatin, pitavastatin and fluvastatin); treatment of patients with HIV co-infection; hepatic impairment; HCV/HBV co-infection; paediatric population; contains lactose.
Adult dosing	Dasabuvir is administered in combination with ombitasvir/paritaprevir/ritonavir, with or without ribavirin. The recommended dose of dasabuvir is 250 mg (one tablet) twice daily (morning and evening), administered orally.
Recommended duration of treatment	12–24 weeks (depending on viral genotype, patient population and treatment combination).*

* See Table 3.9. bellow
Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; DAA=direct-acting antiviral; EMA=European Medicines Agency; SAE=serious adverse event
Source: SmPC (EMA), last update 30/09/2015 [21]

Table 3.9. Recommended co-administered medicinal product(s) and treatment duration for dasabuvir by patient population, according to EMA

Patient population	**Treatment***	**Duration**
Genotype 1b, without cirrhosis	Dasabuvir + ombitasvir/paritaprevir/ritonavir	12 weeks
Genotype 1b, with compensated cirrhosis	Dasabuvir + ombitasvir/paritaprevir/ritonavir + ribavirin	12 weeks
Genotype 1a, without cirrhosis	Dasabuvir + ombitasvir/paritaprevir/ritonavir + ribavirin*	12 weeks
Genotype 1a, with compensated cirrhosis	Dasabuvir + ombitasvir/paritaprevir/ritonavir + ribavirin*	24 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
Abbreviations: EMA=European Medicines Agency
Source: SmPC (EMA), last update 30/09/2015 [21]

Serious adverse effects listed in Micromedex are:
hematologic: decreased hemoglobin, grade 3 or 4 (grade 3, 0.1% to 0.8%; grade 4, 0.3%) and **hepatic**: ALT/SGPT level raised, grade 3 or 4 (0.2% to 1.1%), increased bilirubin level, grade 3 or 4 (0.1% to 9.7%)[3].

Comparators (peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, telaprevir, boceprevir)

Peginterferon alfa-2a

Peginterferon alfa-2a is a covalent conjugate of the protein interferon alfa-2a and polyethylene glycol (PEG) reagent, which acts as a crucial mediator of the innate antiviral immune response. Peginterferon alfa-2a is produced by recombinant DNA technology in *Escherichia coli*, at a degree of substitution of one mole of polymer per mole of protein. The average molecular mass is approximately 60,000 of which the protein moiety constitutes approximately 20,000.

Peginterferon alfa-2a binds to the human type 1 interferon receptor. On receptor dimerisation, multiple intracellular signal transduction pathways are activated, initially mediated by the JAK/STAT pathway.

Peginterferon alfa-2a is indicated in combination with other medicinal products for the treatment of CHC in adult patients with compensated liver disease.

Peginterferon alfa-2a is authorised for use in the EU as well as in the US (as a medicinal product under the proprietary name Pegasys).

The treatment regimen implies weekly subcutaneous administration of peginterferon alfa-2a, in both treatment-naive adult patients and treatment-experienced adult patients. Peginterferon alfa-2a can be used as monotherapy, bitherapy with ribavirin or triple therapy (with ribavirin and telaprevir or simeprevir or sofosbuvir).

The efficacy of peginterferon alfa-2a monotherapy and combination therapy was investigated in numerous studies in adult, treatment-naive patients with CHC.

Summary data on peginterferon alfa-2a, according to EMA, may be found in Table 3.10.

Further details on administration and dosing, according to EMA, may be found in Appendix 1.

Table 3.10. Summary data on peginterferon alfa-2a, according to EMA

Peginterferon alfa-2a (Pegasys)	
Active substance	peginterferon alfa-2a
ATC code	Immunostimulants, IFNs ATC code: L03AB11
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substance, to alfa interferons, or to any of the drug excipients; autoimmune hepatitis; severe hepatic dysfunction or decompensated cirrhosis of the liver; a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous 6 months; HCV/HIV

Peginterferon alfa-2a (Pegasys)	
	patients with cirrhosis and a Child-Pugh score ≥6, except if only due to indirect hyperbilirubinaemia caused by medicinal products such as atazanavir and indinavir; combination with telbivudine; neonates and young children up to 3 years old, because of the excipient benzyl alcohol; in paediatric patients, the presence of or history of a severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.
SAEs	Bacterial infection (e.g., sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia) (3% in CHC and 5% in CHC/HIV). Other SAEs (frequency of less than 1%): suicide, suicidal ideation, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anaemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, cerebral haemorrhage, thrombotic thrombocytopenic purpura, psychotic disorder, and hallucination.
Special warnings and precautions for use	Psychiatric and central nervous system (CNS): severe CNS effects, particularly depression, suicidal ideation and attempted suicide; other CNS effects including aggressive behaviour (sometimes as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status. Patients with existence or history of severe psychiatric conditions. Patients with substance use or abuse: increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders. Growth and development: children and adolescents. Laboratory tests prior to and during therapy: standard haematological and biochemical laboratory tests, adequately controlled thyroid function (TSH and T4). Endocrine system: thyroid function abnormalities or worsening of pre-existing thyroid disorders, hypoglycaemia, hyperglycaemia, and diabetes mellitus. Cardiovascular system: patients with hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction require close monitoring; electrocardiogram (ECG) prior to initiation of therapy recommended. Liver function. Hypersensitivity: serious, acute hypersensitivity reactions (e.g., urticaria, angio-oedema, bronchoconstriction, anaphylaxis). Autoimmune disease: Vogt-Koyanagi-Harada (VKH) syndrome. Fever/infections. Ocular changes: retinopathy including retinal haemorrhages, cotton wool spots, papilloedema, optic neuropathy and retinal artery or vein obstruction, which may result in loss of vision; a baseline eye examination is recommended. Pulmonary changes: dyspnoea, pulmonary infiltrates, pneumonia, and pneumonitis. Skin disorder: exacerbation or provocation of psoriasis and sarcoidosis. Transplantation. HCV/HIV coinfection. Dental and periodontal disorders. Use of peginterferon as long-term maintenance monotherapy (unapproved use). Excipient (benzyl alcohol).

Peginterferon alfa-2a (Pegasys)	
Adult dosing	Treatment-naive adult patients: 180 microgram once weekly by subcutaneous administration in the abdomen or thigh, given in combination with oral ribavirin or as monotherapy. The ribavirin dose should be administered with food. Treatment-experienced adult patients: 180 microgram once weekly by subcutaneous administration, in combination with ribavirin; the dose of ribavirin is weight-based (<75 kg = 1,000 mg and ≥75 kg = 1,200 mg daily, regardless of genotype).
Recommended duration of treatment	*Duration of treatment – interferon-alfa-naive patients:* *Peginterferon alfa-2a + ribavirin:* Genotype 1, LVL with RVR* : 24 w or 48 w Genotype 1, HVL with RVR*: 48 w Genotype 1 or 4 without RVR*: 48w Genotype 2 or 3 without RVR**: 24 w Genotype 2 or 3, LVL with RVR**: 16 or 24 w Genotype 2 or 3, HVL with RVR**: 24 w Genotype 4 with RVR*: 24 or 48w Patients with genotype 5 and 6: limited available data; 48 weeks recommended. *Duration of treatment – retreatment of prior treatment failures:* 48 weeks, regardless of HCV genotype.

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; CNS=central nervous system; EMA=European Medicines Agency; HIV=human immunodeficiency virus; *RVR = rapid viral response (HCV RNA undetectable) at week 4 and HCV RNA undetectable at week 24; **RVR = rapid viral response (HCV RNA negative) by week 4; LVL=low viral load; SAE=serious adverse event; VKH=Vogt-Koyanagi-Harada; T4= Thyroxine ;TSH= Thyroid-stimulating hormone
Source: SmPC (EMA), last update 29/10/2015 [31]

Serious adverse effects listed in Micromedex are:
cardiovascular: Myocardial infarction, Supraventricular arrhythmia;
dermatologic: Erythroderma, Stevens-Johnson syndrome;
gastrointestinal: Colitis (less than 1%), Gastrointestinal hemorrhage (less than 1%), Pancreatitis (less than 1%);
hematologic: Anemia (2% to 14%), Aplastic anemia (less than 1%), Cytopenia, Lymphocytopenia (3% to 14%), Neutropenia (21% to 40%), Thrombocytopenia (5% to 8%), Thrombotic thrombocytopenic purpura (less than 1%);
hepatic: Graft rejection, Liver, Liver failure;
immunologic: Autoimmune disease (less than 1%), Graft rejection, Liver, Graft rejection, Renal, Hypersensitivity reaction;
musculoskeletal: Myositis (less than 1%);
neurologic: Cerebral hemorrhage (less than 1%), Cerebral ischemia, Coma (less than 1%), Peripheral neuropathy (less than 1%), Seizure;
ophthalmic: Corneal ulcer (less than 1%), Retinal hemorrhage, Serous retinal detachment, Thrombosis of retinal artery, Thrombosis of retinal vein;
psychiatric: Depression (18% to 20%), Psychotic disorder (Less than 1%), Suicide;
r**enal:** Graft rejection, Renal;
respiratory: Pulmonary embolism (less than 1%);
other: Bacterial infectious disease (5% or less), Infectious disease[3].

Peginterferon alfa-2b

Peginterferon alfa-2b is a recombinant human interferon alfa-2b produced by recombinant DNA technology in *E. coli*. Recombinant interferon alfa-2b is covalently conjugated with monomethoxy PEG at an average degree of substitution of 1 mole of polymer per mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

Peginterferon alfa-2b bonds to the receptors on cell membranes and initiates a complex sequence of intracellular events that include the induction of certain enzymes. It thereby induces various cellular responses specific to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and numerous immunomodulating activities (e.g., it enhances the phagocytic activity of macrophages and increases the specific cytotoxicity of lymphocytes for target cells). Recombinant interferon alfa-2b also inhibits viral replication both *in vitro* and *in vivo*. The exact antiviral mechanism of action is unknown, but it appears that peginterferon alfa-2b alters the host cell metabolism. This action inhibits viral replication or, if replication occurs, the progeny virions are unable to leave the cell.

Peginterferon alfa-2b can be used for CHC infection treatment as monotherapy, bitherapy (with ribavirin) or tritherapy (with ribavirin boceprevir and simeprevir).

As monotherapy, peginterferon alfa-2b is indicated for the treatment of adult patients (18 years of age and older) with CHC who are positive for hepatitis C virus RNA (HCV RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV. Interferon monotherapy, including peginterferon alfa-2b, is indicated mainly in cases of intolerance or contraindication to ribavirin.

As bitherapy, peginterferon alfa-2b is indicated for the treatment of CHC infection in adult patients who are previously untreated. This includes patients with clinically stable HIV co-infection and patients for whom previous treatment with interferon-alfa (pegylated or non-pegylated) and ribavirin combination therapy or interferon alfa monotherapy has failed.

As tritherapy, peginterferon alfa-2b is indicated, in combination with ribavirin and boceprevir, for the treatment of CHC genotype 1 infection in adult patients (18 years of age and older) with compensated liver disease who are previously untreated or for whom previous therapy failed.

Peginterferon alfa-2b is authorised for use in the EU (as a medicinal product under the proprietary names PegIntron and ViraferonPeg) as well as in the US (as PegIntron).

Peginterferon alfa-2b is administered in weekly dose regimens by subcutaneous injection. The dose administered in adults depends on whether it is used in combination therapy (bitherapy or tritherapy) or as monotherapy.

Clinical efficacy and safety of peginterferon alfa-2b monotherapy or combination therapy was examined in numerous clinical trials conducted in adult naive patients.

Summary data on peginterferon alfa-2b, according to EMA, may be found in Table 3.11.

Further details on administration and dosing, according to EMA, may be found in Appendix 1.

Table 3.11. Summary data on peginterferon alfa-2b, according to EMA

Peginterferon alfa-2b (PegIntron; ViraferonPeg)	
Active substance	peginterferon alfa-2b
ATC code	Immunostimulants, interferons; ATC code: L03AB10

Peginterferon alfa-2b (PegIntron; ViraferonPeg)	
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substance or to any interferon or to any of the drug excipients. A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous 6 months; severe, debilitating medical conditions; autoimmune hepatitis or a history of autoimmune disease; severe hepatic dysfunction or decompensated cirrhosis of the liver; pre-existing thyroid disease unless it can be controlled with conventional treatment; epilepsy and/or compromised central nervous system (CNS) function; HCV/HIV patients with cirrhosis and a Child-Pugh score ≥6; combination of PegIntron with telbivudine. Contraindications related to ribavirin and boceprevir.
SAEs	Arrhythmia, cardiomyopathy, cardiac arrest. Depression, suicidal ideation, suicide. Severe neutropenia (WHO grade 3 and WHO grade 4). Retinopathies (including macular oedema, retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema). Autoimmune and immune-mediated disorders (thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies, and Vogt-Koyanagi-Harada syndrome).
Special warnings and precautions	Psychiatric and CNS: severe CNS effects, particularly depression, suicidal ideation and attempted suicide; other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status). Patients with existence or history of severe psychiatric conditions. Patients with substance use or abuse (increased risk of developing psychiatric disorders or exacerbation of already existing psychiatric disorders). Growth and development (children and adolescents). Acute hypersensitivity (e.g., urticaria, angio-oedema, bronchoconstriction, anaphylaxis). Cardiovascular system (adult patients with a history of congestive heart failure, myocardial infarction, and/or previous or current arrhythmic disorders require close monitoring). Hepatic failure; pyrexia; hydration; pulmonary changes (pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality). Autoimmune disease: Vogt-Koyanagi-Harada (VKH) syndrome. Ocular changes (retinal haemorrhages, retinal exudates, serous retinal detachment, and retinal artery or vein occlusion; a baseline eye examination is recommended). Thyroid changes (hypothyroidism or hyperthyroidism). Metabolic disturbances (hypertriglyceridaemia and aggravation of hypertriglyceridaemia; monitoring of lipid levels is recommended). HCV/HIV co-infection (Mitochondrial toxicity and lactic acidosis, Hepatic

Peginterferon alfa-2b (PegIntron; ViraferonPeg)	
	decompensation in HCV/HIV co-infected patients with advanced cirrhosis, Haematological abnormalities, Patients with low CD4 counts); dental and periodontal disorders; organ transplant recipients; psoriatic disease, and sarcoidosis. Laboratory tests prior to and during therapy: standard haematological (platelets, neutrophil count) and biochemical laboratory tests, adequately controlled thyroid function (TSH). PegIntron should not be used as long term maintenance monotherapy. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucraseisomaltase insufficiency should not take this medicine.
Adult dosing	Monotherapy: 0.5 or 1.0 microgram/kg/week, administered by subcutaneous injection. *Bitherapy (PegIntron with ribavirin):* PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules. *Tritherapy (PegIntron with ribavirin and boceprevir):* applies to adult patients with genotype 1 CHC.
Recommended duration of treatment	Bitherapy: *Naive patients* Patients with genotype 1: 24–48 weeks Patients with genotype 2 and 3: 24 weeks, except for HCV/HIV co-infected patients 48 weeks Patients with genotype 4: 24–48 weeks *Adults - Duration of treatment - HCV/HIV co-infection* *Bitherapy:* The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks regardless of genotype. *Retreatment of prior treatment failures:* 48 weeks, regardless of HCV genotype. Monotherapy: 6 months–1 year Tritherapy (data available from Boceprevir SmPC) Patients without cirrhosis: Treatment-naive patients: 28-48 weeks Patients for whom previous therapy failed: 48 weeks All cirrhotic patients and null responders: 48 weeks Poor interferon-responsive patients: case by case basis

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; CNS=central nervous system; EMA=European Medicines Agency; HIV=human immunodeficiency virus; SAE=serious adverse event; VKH=Vogt-Koyanagi-Harada; WHO=World Health Organization.
Source: SmPC (EMA), last update 22/19/2015 [24]

Serious adverse effects listed in Micromedex are:
Cardiovascular: Bundle branch block, Cardiomyopathy, Hypotension, Myocardial infarction, Supraventricular arrhythmia, Ventricular tachycardia;
Gastrointestinal: Colitis, Pancreatitis (hepatitis C virus [combination therapy], less than 1%);
Hematologic: Anemia (hepatitis C virus [combination therapy], 12%; hepatitis C virus

(monotherapy, pediatric) 11%), Thrombocytopenia (hepatitis C virus (monotherapy), 7%; hepatitis C virus (combination therapy), 5%);
Neurologic: Encephalopathy; Ophthalmic: Blindness AND/OR vision impairment level (melanoma, less than 1%; hepatitis C virus (combination therapy), less than 1%), Optic neuritis (hepatitis C virus (combination therapy), less than 1%), Retinal hemorrhage, Thrombosis of retinal vein (hepatitis C virus (combination therapy), less than 1%);
Psychiatric: Aggressive behavior, Bipolar disorder, Depression (Melanoma, 59%; hepatitis C virus (monotherapy), 29%; hepatitis C virus (combination therapy), 31%), Hallucinations, Homicidal thoughts, Suicidal thoughts, Suicide. Postmarketing data: Hallucinations, possibly life threatening or fatal, have been reported in postmarketing experience[3].

Ribavirin

Ribavirin is a synthetic nucleoside analogue which exerts *in vitro* activity against some RNA and DNA viruses. Ribavirin is indicated in bitherapy combination with peginterferon alfa-2b or interferon alfa-2b or in tritherapy combination with boceprevir and peginterferon alfa-2b. The mechanism by which ribavirin in combination with peginterferon alfa-2b or interferon alfa-2b exerts its effects against HCV is unknown. There is no safety or efficacy information on the use of ribavirin with other forms of interferon (i.e., not alfa-2b).

As tritherapy, ribavirin in combination with boceprevir and peginterferon alfa-2b is indicated for the treatment of CHC-genotype-1 infection in adult patients with compensated liver disease who are previously untreated or for whom previous therapy failed.

As bitherapy, ribavirin is indicated for the treatment of CHC-virus infection in adults, children 3 years of age and older and adolescents and must only be used as part of a combination regimen with peginterferon alfa-2b or interferon alfa-2b.

Ribavirin monotherapy must not be used.

Ribavirin combination therapy is indicated for treatment of adult patients, both naïve and previously treated, as follows:

In adult naive patients ribavirin is indicated as:

- tritherapy – in combination with peginterferon alfa and boceprevir or telaprevir or simeprevir or sofosbuvir for the treatment of adult patients with CHC-genotype-1 infection; in combination with ombitasvir + paritaprevir + ritonavir/dasabuvir for the treatment of adult patients with CHC-genotype-1 infection; in combination with daclatasvir and peginterferon alfa for the treatment of adult patients with CHC-genotype-4 infection.
- bitherapy – in combination with interferon alfa-2b or peginterferon alfa-2b, for the treatment of adult patients with CHC, not previously treated, without liver decompensation, with elevated ALT, who are positive for hepatitis C viral RNA (HCV RNA).
- bitherapy – for the treatment of CHC infection in combination with peginterferon alfa-2b for patients with compensated cirrhosis and/or clinically stable HIV co-infection.

In previously-treated adult patients ribavirin is indicated as:

- tritherapy – in combination with peginterferon alfa-2b and boceprevir for the treatment of adult patients having CHC-genotype-1 infection with compensated liver disease.
- bitherapy – in combination with peginterferon alfa-2b, for the treatment of patients with CHC for whom previous treatment with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin failed.
- bitherapy – in combination with interferon alfa-2b, for the treatment of patients with CHC who have previously responded (with normalisation of ALT at the end of treatment) to interferon alfa monotherapy but who have subsequently relapsed.

- bitherapy – in combination with sofosbuvir+ledipasvir for the treatment of adult patients with CHC-genotype-1, 3 and 4 infection; in combination with ombitasvir + paritaprevir + ritonavir for the treatment of adult patients with CHC-genotype-4 infection.

Ribavirin has authorised for use in both the EU and US markets (proprietary name Rebetol). In the EU, three generic ribavirin medicines are authorised: Ribavirin Mylan, Ribavirin Teva, and Ribavirin Teva Pharma B.V.

Dose regimens imply daily oral administration of ribavirin in two doses. Numerous clinical trials evaluated clinical efficacy and safety of ribavirin combination therapy. Summary data on ribavirin, according to EMA, may be found in Table 3.12. Further details on administration and dosing, according to EMA, may be found in Appendix 1.

Table 3.12. Summary data on ribavirin, according to the EMA

Ribavirin (Rebetol and generics)	
Active substance	ribavirin
ATC code	DAAs, nucleosides and nucleotides (excluding. reverse transcriptase inhibitors); ATC code: J05AB04
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substance or to any of the drug excipients. Pregnant women (ribavirin must not be initiated until a negative pregnancy test result has been obtained immediately prior to initiation of therapy). Lactation. A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous 6 months. Patients with severe, debilitating medical conditions. Patients with chronic renal failure, patients with creatinine clearance <50 ml/minute and/or on haemodialysis. Severe hepatic impairment (Child-Pugh Classification B or C) or decompensated cirrhosis of the liver. Haemoglobinopathies (e.g., thalassaemia, sickle-cell anaemia). Initiation of peginterferon alfa-2b is contraindicated in HCV/HIV patients with cirrhosis and a Child-Pugh score ≥6. For co-administration with peginterferon alfa-2b or interferon alfa-2b: - Autoimmune hepatitis or history of autoimmune disease.
SAEs	Severe depression and suicidal or homicidal ideation, suicide attempt, cardiac arrest, haemolytic anaemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Severe neutropenia (WHO grade 3 and WHO grade 4); WHO grade 3 leukopenia.
Special warnings and precautions	Psychiatric and central nervous system (severe CNS effects, particularly depression, suicidal ideation and attempted suicide, aggressive behaviour sometimes directed against others such as homicidal ideation, bipolar disorder, mania, confusion, and alterations of mental status); patients with existence or

Ribavirin (Rebetol and generics)	
	history of severe psychiatric conditions: patients with substance use or abuse. Haemolysis may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Cardiovascular: adult patients with a history of congestive heart failure, myocardial infarction, and/or previous or current arrhythmic disorders. Acute hypersensitivity: ocular changes (retinopathy including retinal haemorrhages, retinal exudates, papilloedema, optic neuropathy, and retinal artery or vein occlusion, which may result in loss of vision); liver function; potential to exacerbate immunosuppression: pancytopenia and bone marrow suppression; thyroid supplemental monitoring specific for children and adolescents; HCV/HIV co-infection; dental and periodontal disorders; standard haematologic tests and blood chemistries must be conducted in all patients prior to initiating therapy; use in patients with rare hereditary disorders.
Adult dosing	The recommended dose of ribavirin ranges from 800 to 1400 mg, depending on patient body weight. Ribavirin capsules are to be administered orally each day in two divided doses (morning and evening) and with food. Ribavirin must be used in combination with either peginterferon alfa-2b (1.5 microgram/kg/week) or interferon alfa-2b (3 million international units [MIU] three times a week). In tritherapy, ribavirin is co-administered with boceprevir, 800 mg administered orally three times daily (TID) with food (a meal or light snack).
Recommended duration of treatment	Bitherapy with peginterferon alfa-2b: - Treatment-naive patients: HCV genotype 1 for 48 weeks; HCV genotypes 2 and 3 for 24 weeks - Patients who have failed previous therapy: 48 weeks regardless of HCV genotype Bitherapy with peginterferon alfa-2b: - Treatment-naive patients: 24–48 weeks - Patients for whom previous therapy failed: 24 weeks Tritherapy with boceprevir and peginterferon alfa-2b: - Patients without cirrhosis: - Treatment-naive patients: 28–48 weeks - Patients for whom previous therapy failed: 48 weeks - All cirrhotic patients and null responders: 48 weeks - Poor interferon-responsive patients: case by case basis

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; CNS=central nervous system; DAA=direct-acting antiviral; EMA=European Medicines Agency; HIV=human immunodeficiency virus; MIU=million international units; SAE=serious adverse event; TID=three times daily; WHO=World Health Organization
Source: SmPC (EMA), last update 10/06/2015 [32]

Serious adverse effects listed in Micromedex are:

Cardiovascular: Myocardial infarction;
Hematologic: Hemolytic anemia (10% to 13%), Thrombotic thrombocytopenic purpura (<1%);
Hepatic: Hepatotoxicity, Hyperammonemia, Hyperbilirubinemia, Increased erythrocyte destruction, Liver failure, oral, in combination with peginterferon alfa-2a (2%);
Immunologic: Bacterial infectious disease, oral, in combination with peginterferon alfa-2a (less than 1%);
Psychiatric: Suicide (Less than 1%);

Respiratory: Complication of respiratory therapy procedure, Drug precipitation, Respiratory complication[3].

Ribavirin – generic medicines

All ribavirin generic medicines (Ribavirin Mylan, Ribavirin Teva, and Ribavirin Teva Pharma B.V.) are indicated for the treatment of CHC infection in adults, children 3 years of age or older and adolescents, and must only be used as part of a combination regimen with interferon alfa-2b. Ribavirin monotherapy must not be used.

There is no safety or efficacy information on the use of ribavirin with other forms of interferon (i.e., not alfa-2b).

All ribavirin generic medicines, in combination with interferon alfa-2b, are indicated for the treatment of adult naive patients with all types of CHC except genotype 1, not previously treated, without liver decompensation, with elevated ALT, and who are positive for HCV RNA. These medicines are also indicated, in combination with interferon alfa-2b, for the treatment of adult patients with CHC who have previously responded (with normalisation of ALT at the end of treatment) to interferon alfa monotherapy but who have subsequently relapsed.

Further details on administration and dosing, according to EMA, may be found in Appendix 1.

Telaprevir

Telaprevir is a potent, slow-binding inhibitor that blocks the action of an enzyme HCV NS3-4A protease in the HCV.

Telaprevir, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype-1 CHC in adult patients with compensated liver disease (including cirrhosis), who are treatment-naive or who have previously been treated with interferon-based treatment (interferon alfa [pegylated or non-pegylated] alone or in combination with ribavirin), including prior null responders, partial responders, and relapsers.

Telaprevir is authorised for use in the EU (INCIVO®) as well as in the US (INCIVEK^{TM}).Vertex Pharmaceuticals discontinued the sales and marketing of INCIVEK® (telaprevir) in the United States on October 16, 2014[3].

Dosing regimens include daily administration, with a maximum daily dose of 2,250 mg divided into two portions or three portions (taken every 8 hours; q8h). Telaprevir should be administered in conjunction with ribavirin and either peginterferon alfa-2a or alfa-2b. Treatment that is discontinued because of adverse drug reactions or insufficient virologic response should not be reinitiated.

Summary data on telaprevir, according to EMA, may be found in Table 3.13.

Further details on administration and dosing, according to EMA, may be found in Appendix 1.

Table 3.13. Summary data on telaprevir, according to EMA

Telaprevir (Incivo)	
Active substance	telaprevir
ATC code	DAA; ATC code: J05AE11
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes

Telaprevir (Incivo)	
Contraindications	Hypersensitivity to the active substance or to any of the excipients in the drug. Concomitant administration with active substances that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g., alfuzosin, amiodarone, bepridil, quinidine, astemizole, terfenadine, cisapride, pimozide, ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), lovastatin, simvastatin, atorvastatin, sildenafil or tadalafil (only when used for treatment of pulmonary arterial hypertension), quetiapine, and orally administered midazolam or triazolam. Concomitant administration with Class Ia or III antiarrhythmics, except for intravenous lidocaine. Concomitant administration of INCIVO with active substances that strongly induce CYP3A, e.g., rifampicin, St John's wort *(Hypericum perforatum*), carbamazepine, phenytoin and phenobarbital and, thus, may lead to lower exposure and loss of efficacy of telaprevir. Contraindications related to peginterferon alfa and ribavirin.
SAEs	Severe, potentially life-threatening and fatal skin reactions (DRESS, SJS, and TEN). Anaemia.
Special warnings and precautions for use	Cardiovascular**:** – Should be used with caution with Class Ic antiarrhythmics propafenone and flecainide. – Caution is recommended for concurrent use with medicinal products known to induce QT prolongation and which are CYP3A substrates (e.g., erythromycin, clarithromycin, telithromycin, posaconazole, voriconazole, ketoconazole, tacrolimus, salmeterol). – Co-administration with domperidone should be avoided. – Use should be avoided in patients with congenital QT prolongation or a family history of congenital QT prolongation or sudden death; in the event that treatment in such patients is judged strictly necessary, patients should be closely monitored, including electrocardiogram (ECG) assessments. – Use with caution in patients with: A history of acquired QT prolongation. Clinically relevant bradycardia (persistent heart rate <50 bpm). A history of heart failure with reduced left-ventricular ejection fraction. A requirement for medicinal products known to prolong the QT interval but the metabolism of which is not mainly CYP3A4-dependent (e.g., methadone). Electrolyte disturbances (e.g., hypokalaemia, hypomagnesaemia, and hypocalcaemia) should be monitored and corrected, if necessary, prior to initiation and during therapy. Pregnancy and contraception requirements (use with ribavirin and peginterferon alfa); severe rash: toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson Syndrome (SJS); anaemia; use in patients with advanced liver disease; laboratory tests. (HCV RNA levels should be monitored at Weeks 4 and 12; complete blood count with white blood cell differential counts, electrolytes, serum creatinine, liver function tests, TSH, uric acid prior to initiating combination treatment). Combination with peginterferon alfa-2b (no data for treatment-experienced patients and limited data for treatment-naive patients); insufficient virologic response; use in treatment of HCV genotypes other than genotype 1). Renal impairment; hepatic impairment; organ transplant patients; HCV/HIV co-infection; HCV/hepatitis B virus (HBV) co-infection; paediatric population; thyroid disease; interactions with medicinal products; important information about some of the ingredients.

Telaprevir (Incivo)	
Adult dosing	Orally, 1,125 mg (three 375 mg film-coated tablets) twice daily with food. Alternatively, 750 mg (two 375 mg tablets) orally every 8 hours (q8h) with food. The total daily dose is six tablets (2,250 mg). Taking telaprevir without food or without regard to the dosing interval may result in decreased plasma concentrations of telaprevir, which could reduce the therapeutic effect. Telaprevir should be administered in conjunction with ribavirin and either peginterferon alfa-2a or alfa-2b.
Recommended duration of treatment	12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on viral response and prior response status.

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; DAA=direct-acting antiviral; DRESS=drug rash with eosinophilia and systemic symptoms; ECG=electrocardiogram; EMA=European Medicines Agency; HBV=hepatitis B virus; HIV=human immunodeficiency virus; SAE=serious adverse event; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis
Source: SmPC (EMA)[26]

Serious adverse effects listed in Micromedex are:
dermatologic: Stevens-Johnsonov syndrome (less tham 1%), toxic epidermal necrolysis;
hematologic: anemia (36%);
immunologic: drug hypersensitivity syndrome (less than 1%)[3].

Boceprevir

Boceprevir is an inhibitor of the HCV NS3 protease. The HCV NS3-4A protease catalyses the proteolytic cleavage of the HCV-encoded polyprotein into mature forms of the NS4A, NS4B, NS5A and NS5B proteins. Boceprevir covalently, yet reversibly, binds to the NS3 protease active site serine (Ser139) through an (alfa)-ketoamide functional group to inhibit viral replication in HCV-infected host cells. In a biochemical assay, boceprevir acted as an inhibitor of recombinant HCV genotype 1a and 1b NS3-4A protease enzymes.

Boceprevir is indicated for the treatment of CHC genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are previously untreated or for whom previous therapy failed.

Boceprevir is authorised for use in both the EU and US under the proprietary name Victrelis**.**

The manufacture and distribution of Victrelis(R) is being voluntarily discontinued by Merck Sharp & Dohme as of December 31, 2015 due to a business decision and not because of safety or efficacy findings associated with the product[3].

Boceprevir must be administered in combination with peginterferon alfa and ribavirin, with a maximum daily dose divided into three portions.

Summary data on boceprevir, according to EMA, may be found in Table 3.14.

Further details on administration and dosing, according to EMA, may be found in Appendix 1.

Table 3.14. Summary data on boceprevir, according to EMA

Boceprevir (Victrelis)	
Active substance	boceprevir
ATC code	Antivirals for systemic use, protease inhibitors; ATC code: J05AE12

Boceprevir (Victrelis)	
Approved indication in chronic hepatitis C (CHC) infection in adults	Yes
Contraindications	Hypersensitivity to the active substance or any of the excipients in the drug. In patients with autoimmune hepatitis. Co-administration with medicines that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam and triazolam, bepridil, pimozide, lumefantrine, halofantrine, tyrosine kinase inhibitors, simvastatin, lovastatin, quetiapine, alfuzosin, silodosin, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine). Pregnancy. Contraindications related to peginterferon alfa and ribavirin.
SAEs	Grade 3-4 neutropenia; serious, acute hypersensitivity reactions.
Special warnings and precautions for use	Anaemia; neutropenia; pancytopenia; hypersensitivity; patients with advanced liver disease; drospirenone-containing medicines; HCV protease monotherapy not recommended (because of the high probability of increased resistance without combination anti-HCV therapies); laboratory testing necessary for HCV RNA levels monitoring and complete blood counts; use in patients with HIV co-infection; use in patients with HBV co-infection; use in patients with an organ transplant; use in patients having HCV genotypes other than genotype 1; use in patients for whom previous treatment with an HCV protease inhibitor failed; the concomitant use of boceprevir with potent CYP3A4 inducers (rifampicin, carbamazepine, phenobarbital, phenytoin); co-administration with alfuzosin and silodosin is contraindicated; the concomitant use with doxazosin and tamsulosin is not recommended; use in patients with rare hereditary disorders; proarrhythmic effects: caution in patients at risk of QT prolongation (long congenital QT, hypokalaemia).
Adult dosing	The recommended dose is 800 mg administered orally three times daily (TID) with food. The maximum daily dose is 2,400 mg. Each hard capsule contains 200 mg of boceprevir. Administration without food could be associated with a net loss of efficacy due to sub-optimal exposure. Must be administered in combination with peginterferon alfa and ribavirin.
Recommended duration of treatment	Patients without cirrhosis: Treatment-naive patients: 28–48 weeks Patients for whom previous therapy failed: 48 weeks All cirrhotic patients and null responders: 48 weeks Poor interferon-responsive patients: case by case basis

Abbreviations: ATC=Anatomical Therapeutic Chemical; CHC=chronic hepatitis C; EMA=European Medicines Agency; HBV=hepatitis B virus; HIV=human immunodeficiency virus; SAE=serious adverse event; TID=three times daily
Sources: SmPC (EMA), last update 09/03/2015 [27]

Serious adverse effects listed in Micromedex are:
dermatologic: drug hypersensitivity syndrome, erythroderma, Stevens-Johnsonov syndrome;
hematologic: anemia (45%-50%), neutropenia (14%-25%), pancytopenia;
immunologic: hypersensitivity reaction[3].

[A0020] For which indications have sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators received marketing authorisation?

A short summary of the regulatory status of the interventions (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) and comparators (peginterferon alfa-2a, peginterferon alfa-2b, ribavirin, telaprevir and boceprevir) by EMA and FDA in CHC infection in adults may be found in Appendix 2, Table A118.

Sofosbuvir

The EMA Committee for Medicinal Products for Human Use (CHMP) recommended marketing authorisation for the medicinal product sofosbuvir, 400 mg, film-coated tablet intended for the treatment of CHC on 21 November 2013. The European Commission granted a marketing authorisation for sofosbuvir valid throughout the EU on 16 January 2014.

Sofosbuvir is indicated in combination with other medicinal products for the treatment of CHC in adults. Sofosbuvir, in different treatment combinations, is used as treatment for all six HCV genotypes (see Table 3.15.).

Table 3.15. Recommended co-administered medicinal product(s) and treatment duration for sofosbuvir combination therapy, according to EMA

Patient population*	Treatment	Duration
Patients with genotype 1, 4, 5 or 6 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks
	Sofosbuvir + ribavirin Only for use in patients ineligible or intolerant to peginterferon alfa	24 weeks
Patients with genotype 2 CHC	Sofosbuvir + ribavirin	12 weeks
Patients with genotype 3 CHC	Sofosbuvir + ribavirin + peginterferon alfa	12 weeks
	Sofosbuvir + ribavirin	24 weeks
Patients with CHC awaiting liver transplantation	Sofosbuvir + ribavirin	Until liver transplantation

* Includes patients co-infected with human immunodeficiency virus (HIV)
Abbreviations: CHC=chronic hepatitis C; EMA=European Medicines Agency; HIV= human immunodeficiency virus
Source: SmPC (EMA)[16]

EMA noted some limitations to the treatments for different HCV genotypes:

> *Treatment-experienced patients with genotype 1, 4, 5, and 6 HCV infection: no optimal treatment duration has been established. Possibility of extended therapy with sofosbuvir, peginterferon alfa and ribavirin beyond 12 weeks and up to 24 weeks should be considered, especially for those subgroups that have one or more factors historically associated with lower response rates to interferon-based therapies (advanced fibrosis/cirrhosis, high baseline viral concentrations, black race, IL28B non CC genotype).*
>
> *Treatment of patients with genotype 5 or 6 HCV infection: only limited data are available.*
>
> *IFN-free therapy for genotype 1, 4, 5, and 6 HCV infection: optimal regimen and treatment duration have not been established and therefore such regimens should only be used for patients who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment.*

In the US, the FDA approved sofosbuvir tablets for the treatment of CHC infection as a component of a combination antiviral treatment regimen on 06 December 2013. Sofosbuvir is indicated for the treatment of CHC infection as a component of a combination antiviral treatment regimen. The FDA determined that sofosbuvir efficacy has been established in subjects with HCV genotype 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection[3].

Ledipasvir + sofosbuvir

According to the EMA, sofosbuvir plus ledipasvir is indicated for the treatment of CHC in adults with genotypes 1, 3, and 4 (see Table 3.16.).

Table 3.16. Recommended treatment duration for sofosbuvir plus ledipasvir and the recommended use of co-administered ribavirin for certain subgroups, according to EMA

Patient population	Treatment	Duration
Patients with genotype 1 or genotype 4 CHC		
Patients without cirrhosis	Sofosbuvir + ledipasvir	12 weeks – 8 weeks may be considered in previously untreated genotype 1-infected patients – 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options
Patients with compensated cirrhosis	Sofosbuvir + ledipasvir	24 weeks – 12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options
Patients with decompensated cirrhosis or who are pre-/post-liver transplant	Sofosbuvir + ledipasvir + ribavirin	24 weeks
Patients with genotype 3 CHC		
Patients with cirrhosis and/or prior treatment failure	Sofosbuvir + ledipasvir + ribavirin	24 weeks

Abbreviations: CHC=chronic hepatitis C; EMA=European Medicines Agency
Source: SmPC (EMA)[17]

EMA noted that only limited clinical data are available on the use in patients infected with HCV genotype 3 and 4 and a conservative 24 weeks of therapy is advised in all treatment-experienced genotype 3 patients and those treatment-naive genotype 3 patients with cirrhosis. Furthermore, efficacy of ledipasvir/sofosbuvir has not been studied in HCV genotype 2, 5, and 6; therefore, sofosbuvir plus ledipasvir should not be used in patients infected with these genotypes.

The CHMP issued a positive opinion on granting a marketing authorisation for sofosbuvir plus ledipasvir, (ledipasvir 90 mg/sofosbuvir 400 mg, film-coated tablet, intended for CHC in adults on 25 September 2014).

The CHMP considered that treatment with sofosbuvir plus ledipasvir, with or without ribavirin, is highly beneficial to many patients with HCV, including those who have had a liver transplant and/or who have compensated cirrhosis. Although studies are limited in patients with decompensated cirrhosis, it was noted that those patients may also benefit from extended treatment with sofosbuvir plus ledipasvir and ribavirin.

The European Commission granted a marketing authorisation for sofosbuvir plus ledipasvir valid throughout the EU on 17 November 2014.

The FDA approved sofosbuvir plus ledipasvir for treatment of chronic HCV genotype 1 infection in adults on 10 October 2014. Sofosbuvir plus ledipasvir was the first combination pill approved by the FDA for chronic HCV genotype 1 treatment and was also the first approved regimen that does not require administration with interferon or ribavirin. Now is approved for treatment of chronic HCV genotype 1, 4,5 or 6 infection in adults [3].

Simeprevir

Simeprevir is indicated for the treatment of CHC, genotype 1 and 4, in adult patients in combination with other medicinal products (peginterferon alfa + ribavirin or sofosbuvir ± ribavirin.). It is not recommended for treatment of patients with HCV genotypes 2, 3, 5, or 6 since the efficacy of simeprevir has not been studied in those patients (see Table 3.17.).

Table 3.17. Recommended co-administered medicinal product(s) and treatment duration for simeprevir combination therapy, according to EMA

Patient population	Treatment	Duration
Treatment-naive, prior relapse[1] and prior non-responder[2] patients (including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection	Simeprevir + sofosbuvir (± ribavirin)[3]	12 weeks[4]
Treatment-naive and prior relapse[1] patients with HCV genotype 1 or 4		
with or without cirrhosis, who are not co-infected with HIV without cirrhosis, who are co-infected with HIV	Simeprevir + peginterferon alfa + ribavirin[5]	24 weeks[6] Treatment with simeprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 12 weeks of peginterferon alfa and ribavirin.
with cirrhosis, who are co-infected with HIV	Simeprevir + peginterferon alfa + ribavirin[5]	48 weeks[6] Treatment with simeprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin.
Prior non-responder[2] patients (including partial and null responders) with HCV genotype 1 or 4, with or without cirrhosis, with or without HIV co-infection	Simeprevir + peginterferon alfa + ribavirin[5]	48 weeks[6] Treatment with simeprevir must be initiated in combination with peginterferon alfa and ribavirin and administered for 12 weeks and then followed by an additional 36 weeks of peginterferon alfa and ribavirin.

[1] Relapse following prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin
[2] Non-response following prior treatment with interferon (pegylated or non-pegylated), with or without ribavirin[3]
Ribavirin could be added based on a clinical assessment of each individual patient. The recommended treatment duration is 12 weeks. A longer treatment duration (up to 24 weeks) of simeprevir with sofosbuvir (with or without ribavirin) could be considered based on an individual basis.
[4] No stopping rules apply to the combination of simeprevir with sofosbuvir.
[5] When considering simeprevir combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, testing for NS3 Q80K polymorphism should be performed before starting treatment
[6] Recommended duration of treatment provided that patient does not meet a stopping rule.
Abbreviations: EMA=European Medicines Agency; HIV=human immunodeficiency virus
Source: SmPC (EMA)[18]

Simeprevir is authorised for use in both the EU and the US.

The CHMP gave a positive opinion and recommended granting a marketing authorisation for the medicinal product simeprevir, 150 mg, hard capsules intended for the treatment of CHC on 20 March 2014. The CHMP concluded that, in both naive patients as well as in previously-treated patients, adding simeprevir to treatment with peginterferon alfa and ribavirin considerably increased the number of patients showing no sign of infection. The data available, which support

the use of simeprevir in combination with sofosbuvir in patients who cannot be given standard treatment including peginterferon alfa, were also taken into consideration.

The European Commission granted a marketing authorisation for simeprevir valid throughout the EU on 14 May 2014.

In the US, the FDA approved simeprevir 150 mg (Olysio®) capsules for the treatment of CHC infection on 22 November 2013. Simeprevir is indicated for use as a component of a combination antiviral treatment regimen. The FDA concluded that the efficacy of simeprevir has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1-infected subjects with compensated liver disease (including cirrhosis). Now it is approved for the treatment of chronic hepatitis C virus (HCV) genotype 1 or 4 in combination with peginterferon alfa plus ribavirin, and for the treatment of HCV genotype 1 infection in adults in combination with sofosbuvir[3].

Daclatasvir

The CHMP recommended granting a marketing authorisation for the medicinal product daclatasvir, 30 and 60 mg, film-coated tablet, intended for the treatment of chronic HCV infection in adults. The European Commission granted a marketing authorisation for daclatasvir valid throughout the EU on 22 August 2014.

Monotherapy of daclatasvir is not recommended. Daclatasvir is indicated in combination with other medicinal products for the treatment of chronic HCV infection in adults (sofosbuvir with or without ribavirin or peginterferon alfa and ribavirin) (see Table 3.18.).

Table 3.18. Recommended regimens and treatment duration for daclatasvir combination therapy, according to EMA

HCV genotype and patient population*	Treatment	Duration
Genotype 1 or 4 without cirrhosis	Daclatasvir + sofosbuvir	12 weeks Consider prolongation of treatment to 24 weeks for patients with prior treatment including an NS3-4A protease inhibitor.
Genotype 1 or 4 compensated cirrhosis	Daclatasvir + sofosbuvir	24 weeks Shortening treatment to 12 weeks may be considered for previously untreated patients with cirrhosis and positive prognostic factors such as IL28B CC genotype and/or low baseline viral load. Consider adding ribavirin for patients with very advanced liver disease or with other negative prognostic factors such as prior treatment experience.
Genotype 3 without cirrhosis	Daclatasvir + sofosbuvir	12 weeks
Genotype 3 with cirrhosis	Daclatasvir + sofosbuvir +/- ribavirin	24 weeks Ribavirin may be added based on clinical assessment of an individual patient.
Genotype 4	Daclatasvir + peginterferon alfa + ribavirin	24 weeks of daclatasvir in combination with 24-48 weeks of peginterferon alfa and ribavirin. If the patient has HCV RNA undetectable at both treatment weeks 4 and 12, all 3 components of the regimen should be continued for a total duration of 24 weeks. If the patient achieves HCV RNA undetectable, but not at both treatment weeks 4 and 12, daclatasvir should be discontinued at 24 weeks and peginterferon alfa and ribavirin continued

		for a total duration of 48 weeks.

* Includes patients co-infected with human immunodeficiency virus (HIV).

Abbreviations: EMA=European Medicines Agency
Source: SmPC (EMA), last updated on 05/11/2015 [19]

EMA also noted some limitations to the treatments for different HCV genotypes:

In patients with genotype 1 infection and compensated cirrhosis, only limited data exist for sofosbuvir in combination with daclatasvir treatment, so there are uncertainties concerning the most appropriate way to use daclatasvir (duration, role of ribavirin) in such patients.

In patients with genotype 2 infection data to support the treatment with daclatasvir and sofosbuvir are limited.

In patients with genotype 3 infection, data support a 12-week treatment duration of daclatasvir + sofosbuvir for treatment-naive and -experienced patients with genotype 3 infection without cirrhosis. Lower rates of SVR were observed for patients with cirrhosis. Data from ongoing compassionate use programmes which included patients with genotype 3 infection and cirrhosis, support the use of daclatasvir + sofosbuvir for 24 weeks in these patients. The relevance of adding ribavirin to that regimen is unclear. In patients with genotype 4 infection, the combination of daclatasvir and sofosbuvir was not studied, but is expected to yield similar activity for genotype 4 as observed for genotype 1, based on in vitro antiviral activity and available clinical data with daclatasvir in combination with peginterferon and ribavirin

In patients with genotype 5 and 6 infection, daclatasvir has not been studied and therefore no regimen recommendation can be given.

In the US, marketing authorisation for daclatasvir was granted by the FDA for treatment of patients with CHC virus genotype 3, in combination with sofosbuvir[3].

Ombitasvir+ paritaprevir + ritonavir

Ombitasvir + paritaprevir + ritonavir is indicated in combination with other medicinal products (dasabuvir or ribavirin or both dasabuvir and ribavirin) for the treatment of CHC in adults (Table 3.19.).

Ombitasvir + paritaprevir + ritonavir is authorised for use in the EU under the proprietary name Viekirax as well as in the US under the proprietary name Technivie and Viekira Pak (ombitasvir + paritaprevir + ritonavir co-packaged with dasabuvir).

The CHMP noted that ombitasvir + paritaprevir + ritonavir, in combination with other medicines, is effective in clearing the HCV genotypes 1a, 1b, and 4, including in patients with liver scarring (Table 3.19.). The clearance rate was particularly high in patients infected with genotypes 1b and 4. The CHMP also noted that although some cases of raised liver enzymes were recorded in patients treated with ombitasvir + paritaprevir + ritonavir in combination with dasabuvir and ribavirin, side effects were generally well tolerated.

The European Commission granted a marketing authorisation valid throughout the EU for ombitasvir + paritaprevir + ritonavir on 15 January 2015.

Table 3.19. Recommended co-administered medicinal product(s) and treatment duration for ombitasvir + paritaprevir + ritonavir by patient population, according to EMA

Patient population	Treatment*	Duration
Genotype 1b, without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1b, with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks

Genotype 1a, without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin*	12 weeks
Genotype 1a, with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin*	24 weeks
Genotype 4, without cirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin	12 weeks
Genotype 4, with compensatedcirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin	24 weeks

* Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
Abbreviations: EMA=European Medicines Agency
Source: SmPC (EMA), last update 28 09 2015[20]

On 19 December 2014, the FDA approved Viekira Pak (ombitasvir + paritaprevir + ritonavir tablets co-packaged with dasabuvir tablets) for treatment of patients with chronic HCV genotype 1 infection, including patients with cirrhosis. Viekira Pak contains ombitasvir + paritaprevir + dasabuvir and also contains ritonavir, a previously approved drug, which is used to increase blood levels of paritaprevir. Viekira Pak can be used with or without ribavirin, but it is not recommended for patients with decompensated cirrhosis.

On 24 July 2015, the FDA approved Technivie (ombitasvir + paritaprevir + ritonavir) for use in combination with ribavirin in patients without scarring and poor liver function (cirrhosis)[3].

Dasabuvir

The EMA CHMP concluded that dasabuvir used in combination with ombitasvir + paritaprevir + ritonavir, with and without ribavirin, is an effective treatment for infections caused by HCV, genotypes 1a and 1b.

The European Commission granted a marketing authorisation for dasabuvir valid throughout the EU on 15 January 2015.

Dasabuvir (Exviera) is indicated in for the treatment of CHC, genotypes 1a and 1b, in adult patients and in combination with other medicinal products used for HCV treatment (ombitasvir + paritaprevir + ritonavir, with or without ribavirin). Dasabuvir is not indicated as monotherapy (Table 3.20.).

Table 3.20. Recommended co-administered medicinal product(s) and treatment duration for dasabuvir by patient population, according to EMA

Patient population	Treatment*	Duration
Genotype 1b, without cirrhosis	Dasabuvir+ombitasvir + paritaprevir + ritonavir	12 weeks
Genotype 1b, with compensated cirrhosis	Dasabuvir+ombitasvir + paritaprevir + ritonavir + ribavirin	12 weeks
Genotype 1a, without cirrhosis	Dasabuvir+ombitasvir + paritaprevir + ritonavir + ribavirin*	12 weeks
Genotype 1a, with compensated cirrhosis	Dasabuvir+ombitasvir + paritaprevir + ritonavir + ribavirin*	24 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
Abbreviations: EMA=European Medicines Agency
Source: SmPC (EMA), last update 30/09/2015[20]

In the US, on 19 December 2014, the FDA granted a marketing authorisation for Viekira Pak (ombitasvir + paritaprevir + ritonavir tablets co-packaged with dasabuvir tablets) to be used in treatment of patients with chronic HCV genotype 1 infection (patients with cirrhosis included). Viekira Pak can be used with or without ribavirin, but it is not recommended for treatment of patients with decompensated cirrhosis[3].

[B0002] What is the claimed benefit of sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir and dasabuvir in relation to the comparators and one in comparison to each other?

Claimed benefits of the DAAs under assessment (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir with or without dasabuvir) over the comparators are improved rates of sustained virologic response (frequently >90%); better efficacy against several HCV genotypes; better safety profiles; shorter treatment duration (12 or 24 weeks), with only oral administration (for those on IFN-free regimens) of once daily combinations or fixed-dose combinations and a lower drug interactions profile. These could improve patient compliance, limit the needs for protracted follow-up, testing and adverse effect management as well as minimise dependence on specialist physicians. Population groups, like those with HCV/HIV infection, liver cirrhosis and liver transplanted patients for HCV-associated liver disease, with previous low response rates or contraindications to treatment with interferon now benefit from the available oral DAA combination therapy[33-38].

[B0004] Who administers sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators and in what context and level of care are they provided?

According to the SmPC, sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir and dasabuvir treatment should be initiated and monitored by a physician experienced in the management of patients with CHC.

Access to a multidisciplinary team is seen as crucial for effective HCV clinical management. The team may usually include: clinician and nursing clinical assessment and monitoring, virology, drug and alcohol services, HIV infection services, psychiatric support for selected cases, pharmacy, and social work and other social support services (including peer support, if available). Measures directed towards increasing adherence are also interdisciplinary. Furthermore, language and comprehension issues should also be taken into account for foreign patients[34].

IFN-containing therapy: peginterferon is administered subcutaneously and is designed for administration by the patient or carer. The doctor or their assistant should instruct the patient or carer on how to give the injections. Each vial should be used by one person only and is for single use. Appropriate training is recommended for non-healthcare professionals administering this medicinal product. The 'Instructions for the User', provided in the carton, must be followed carefully by the patient[24].

[B0008] What kind of special premises are needed for sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir and the comparators?

According to the American Association for the Study of Liver Diseases (AASLD), the Infectious Diseases Society of America (IDSA), and the International Antiviral Society-USA (IAS-USA) (AASLD/IDSA/IAS–USA) 2015 Guidelines[33], all patients with current HCV infection and a positive HCV RNA test result should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (stage F3 or above on the Metavir scale), including possible referral for consideration of liver transplantation.

According to the recommendations of the EASL Guidelines[34]: HCV treatment should be delivered by a multidisciplinary team, with experience in HCV assessment and therapy; HCV-infected patients should be counselled on the importance of adherence for attaining a sustained virological

response (SVR); in patients with socioeconomic disadvantages and in migrants, social support services should be a component of HCV clinical management; in persons who actively inject drugs, access to harm reduction programs is mandatory; peer-based support should be evaluated as a means to improve HCV clinical management; patients should be counselled to abstain from alcohol during antiviral therapy – patients with ongoing alcohol consumption during treatment should receive additional support during antiviral therapy; HCV treatment can be considered also for patients actively using drugs, provided they wish to receive treatment and are able and willing to maintain regular appointments. Also, the potential for drug–-drug interactions involving prescribed and non-prescribed drugs need to be considered.

Treatment monitoring includes monitoring of treatment efficacy and safety, by laboratory assessments and clinical review; therefore, a clinical and laboratory infrastructure is needed for follow-up and monitoring of therapy. During treatment, individuals should be followed up at clinically appropriate intervals to ensure medication adherence, to assess adverse events and potential drug–drug interactions, and to monitor blood test results necessary for patient safety. The frequency and type of contact (e.g., clinic visit, phone call, etc.) are variable but need to be sufficient to assess patient safety and response to treatment. The application of stopping rules when a patient is unlikely to respond to therapy allows the cessation of potentially toxic and expensive therapy. Stopping rules and recommended duration of treatment depends on the stage of disease (cirrhosis versus mild-to-moderate disease), previous treatment failure response (null response, partial response or relapse), genotype and on the results of HCV viral load testing while on treatment. The side-effects profile of peginterferon range from mild to life-threatening, and marked interactions with other medications in patients with co-morbidity are possible. Ribavirin can cause haemolytic anaemia and is teratogenic. Women of childbearing potential and/or their male partners must use an effective form of contraception during treatment and for a period of 6 months after the treatment has concluded. Flu-like symptoms are often present after peginterferon alfa injections; they are easily controlled by paracetamol and tend to attenuate after 4–6 weeks of therapy. At each visit, the patients should be assessed for clinical side effects, such as severe fatigue, depression, irritability, sleeping disorders, skin reactions, and dyspnoea. Thyroxin and thyroid stimulating hormone (TSH) levels should be measured every 12 weeks while on therapy. Haematological side effects of peginterferon alfa and ribavirin include neutropenia, anaemia, thrombocytopenia and lymphopenia; these parameters should be assessed at weeks 1, 2, and 4 of therapy and at 4- to 8-week intervals thereafter.

HCV/HIV-coinfected persons treated with peginterferon and ribavirin and first-generation protease inhibitors (PI) who require HIV therapy should be treated with compatible antiretroviral therapy. They require regular monitoring of CD4 counts during treatment. Regular clinical examination and monitoring of serum bilirubin, albumin and blood clotting profile (the international normalized ratio [INR]) is necessary in persons with cirrhosis on interferon-based treatment in order to detect decompensated disease. The treatment of such persons with IFN-containing regimens carries a higher risk of serious side effects and the use of haemopoietic factors is recommended in settings where these are available[33,34,38].

Treatment of HCV in people who inject drugs requires integration of services, as other health-care needs are often also present. Care should be given only with informed consent[38]. Drug dependency services may be required for the provision of opioid substitution therapy and sterile injection equipment. Alcohol reduction strategies may be required and HIV treatment may also be necessary[38].

According to the WHO Guideline[38], an initial clinical assessment is essential prior to commencing therapy to assess the presence of pre-morbid conditions that may rule out or delay treatment such as severe intercurrent illnesses, for example, tuberculosis, decompensated cirrhosis, or pregnancy. Identifying patients with cirrhosis is of particular importance, as their prognosis is altered and their treatment regimen may be adapted[34]. A psychological assessment at this time and evaluation of potential drug–drug interactions are also essential. Disease education, patient preparation for side effects while on treatment, support and appropriate informed pre- and post-test counselling are required. Access to appropriate diagnostic facilities for toxicity and efficacy monitoring is of critical importance and could be facilitated by utilising the same or similar platforms currently being rolled out for HIV. Management of drug–drug interactions is important, particularly in those infected with HIV[38].

According to the AASLD/IDSA/IAS–USA 2015 Guidelines[33], prior to starting treatment, patients should be evaluated for potential drug–drug interactions with selected antiviral medications. Patients should also be educated on the proper administration of medications (e.g., dose of medications, frequency of taking medicines, with or without food, missed doses, expected duration, adverse effects, etc.), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment.

[A0021] What is the reimbursement status of sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir and dasabuvir?

The reimbursement status of sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir and dasabuvir has already been decided or is currently in process at the national level of Member States.

3.3. Discussion

Some DAAs under assessment have different marketing authorisation status in Europe and the United States (US).

In the US, sofosbuvir is approved for genotypes 1–4. Simeprevir was approved for genotype 1 only but now it is approved for the treatment of chronic hepatitis C virus (HCV) genotype 1 or 4 in combination with peginterferon alfa plus ribavirin, and for the treatment of HCV genotype 1 infection in adults in combination with sofosbuvir. Ledipasvir + sofosbuvir was approved in the US for genotype 1 only but now it is approved for treatment of chronic HCV genotype 1, 4, 5, or 6 infection in adults. The FDA has granted a marketing authorisation for daclatasvir for the treatment of patients with CHC genotype 3 only, in combination with sofosbuvir[3].

Ombitasvir + paritaprevir + ritonavir is authorised for use in the EU under the proprietary name Viekirax. In the US, it is authorised under the proprietary name Technivie (ombitasvir + paritaprevir + ritonavir) and Viekira Pak (ombitasvir + paritaprevir + ritonavir co-packaged with dasabuvir). Viekira Pak is approved for treatment of patients with chronic HCV genotype 1 infection, including patients with cirrhosis. Viekira Pak can be used with or without ribavirin, but it is not recommended for patients with decompensated cirrhosis. Technivie is approved for use in combination with ribavirin for the treatment of HCV genotype 4 infections in patients without cirrhosis[3]. Dasabuvir has centralized marketing authorization by EMA for use in the EU to treat adults with HCV genotype 1.

Vertex Pharmaceuticals discontinued the sales and marketing of INCIVEK® (telaprevir) in the United States on October 16, 2014[3]. The manufacture and distribution of Victrelis® is being voluntarily discontinued by Merck Sharp & Dohme as of December 31, 2015 due to a business decision and not because of safety or efficacy findings associated with the product[3].

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

4.1. Research questions

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment? What is the incidence and prevalence of HCV? Figures in EU if possible per genotype, age group, figures per country. What is the mortality rate for HCV and its complications?
A0023	How many people belong to the target population? Specify, if possible, for each genotype.
A0003	What are the known risk factors for chronic hepatitis C? What are the known risk factors for progression of liver fibrosis? What are the known risk factors for decompensated cirrhosis? What are the known risk factors for hepatocellular carcinoma?
A0004	What is the natural course of the condition?
A0005	What are the symptoms and the burden of disease for the patient? What is the rate of mortality and/or hospitalisation caused by the disease?
A0006	What is the burden of the disease for society?
A0024	How is the health condition currently diagnosed according to published European guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published European guidelines and in practice?
A0007	What is the target population in this assessment?
A0011	How much are the technologies and their comparators utilised?

4.2. Results

Overview of the disease or health condition

[A0002a] What is the disease or health condition in the scope of this assessment?

Hepatitis is an inflammation of the liver, most commonly caused by a viral infection. There are six main hepatitis viruses, referred to as types A, B, C, D, E, and G.

The hepatitis C virus (HCV), initially isolated in 1989[39], was the first virus to be discovered by molecular cloning. HCV is an enveloped virus with a positive-sense, single-stranded ribonucleic acid (RNA) genome with about 9,000 ribonucleotides in the genus *Hepacivirus* of the family *Flaviviridae*[40].

After transmission of the virus, a lower level of HCV RNA concentration in plasma (eclipse phase) persists for 8–24 hours, followed by a period of logarithmic growth. Within 7–21 days after viral transmission, HCV RNA becomes detectable in serum[41]; the incubation period is 30–90 days

approximately. Longer incubation periods can occur in cases where only small amounts of viral load have been transmitted. The viral strain and the amount of the inoculum influence the course of acute hepatitis C only very modestly[42].

HCV infection is infrequently diagnosed during the acute phase because of the lack of symptoms. Even in symptomatic patients most of the clinical signs are non-specific **(A0004)**.

Chronic hepatitis C is marked by the persistence of HCV RNA in the blood for at least 6 months after the onset of acute infection **(A0004)**. Persistent infection relies on rapid production of virus and continuous cell-to-cell spread, along with a lack of vigorous T-cell immune response to HCV antigens.

Genotypes are defined as genetic heterogeneity among different HCV isolates, whereas subtypes are closely related isolates within each of the major genotypes[43]. HCV genotypes differ from each other by up to 35% over the whole viral genome[43].

Agreement on a common genotype classification was reached for the first time in 1994[44]. According to the last available classification[45], seven genotypes and 67 subtypes are confirmed; there are 20 provisionally assigned subtypes and 21 unassigned subtypes. The most recent list is available online (http://talk.ictvonline.org/links/hcv/hcv-classification.htm).

At the European level, the Commission Decision of 28 April 2008[46] defined criteria for identification of HCV, which require detection of HCV nucleic acid in serum *OR* HCV-specific antibody response confirmed by a different antibody test.

[A0002b] What is the incidence and prevalence of HCV? Figures in EU if possible per genotype, age group, figures per country.

Different sources of data are available to estimate the incidence of HCV in Europe, including surveillance systems, prevalence surveys, and expert consensus.

The main reliable data sources for European countries are:

- The European Centre for Disease Prevention and Control (ECDC). The ECDC established a network of national experts from each European Union (EU)/European Economic Area (EEA) country for the enhanced surveillance of hepatitis C following a prevalence survey that identified substantial differences in national systems. Since 2010, the ECDC has promoted the use of The European Surveillance System (TESSy), a web-based platform for data submission, warehousing, and retrieval[47,48]. Duffel et al. have reported results of the first enhanced surveillance data collections of HCV infections across 29 EU/EEA countries[47]. ECDC data provide a partial epidemiological picture of HCV in Europe for the period 2006–2012.
- Reported estimates for 32 countries[49-52].
- Estimates for 22 European countries with an average incidence of acute hepatitis C per 100,000 for the period 1997–2004[53].
- Lavanchy reported 2010 prevalence estimates for different European countries[54].

In 2007, the incidence rate varied between 36.7 cases per 100,000 population (Ireland) and 0.05 per 100,000 population (Greece)[55].

The overall prevalence of hepatitis C in Europe is estimated to be 0.13–3.26%[56] with an annual incidence rate of 6.19 cases (95% CI 4.90–7.48) per 100,000 population[53]. The prevalence of HCV in 2010 as reported by Lavanchy[54], as well as the estimates for 2005[55,57] are within the range reported by Blachier[56].

Many epidemiological studies have confirmed the variability in the prevalence of HCV between countries. The prevalence is estimated at 2.4% (95% CI 2.0–2.8) for Central European countries; 2.9% (95% CI 2.3–3.5) for Eastern European countries; and 2.4% (95% CI 2.2–2.7) for Western European countries[57]. Russia accounts for the largest viraemic population in Europe[50,51,54].

Egypt (14%) and Georgia (6.7%) have the highest prevalence of hepatitis C worldwide and at the European level, respectively[54].

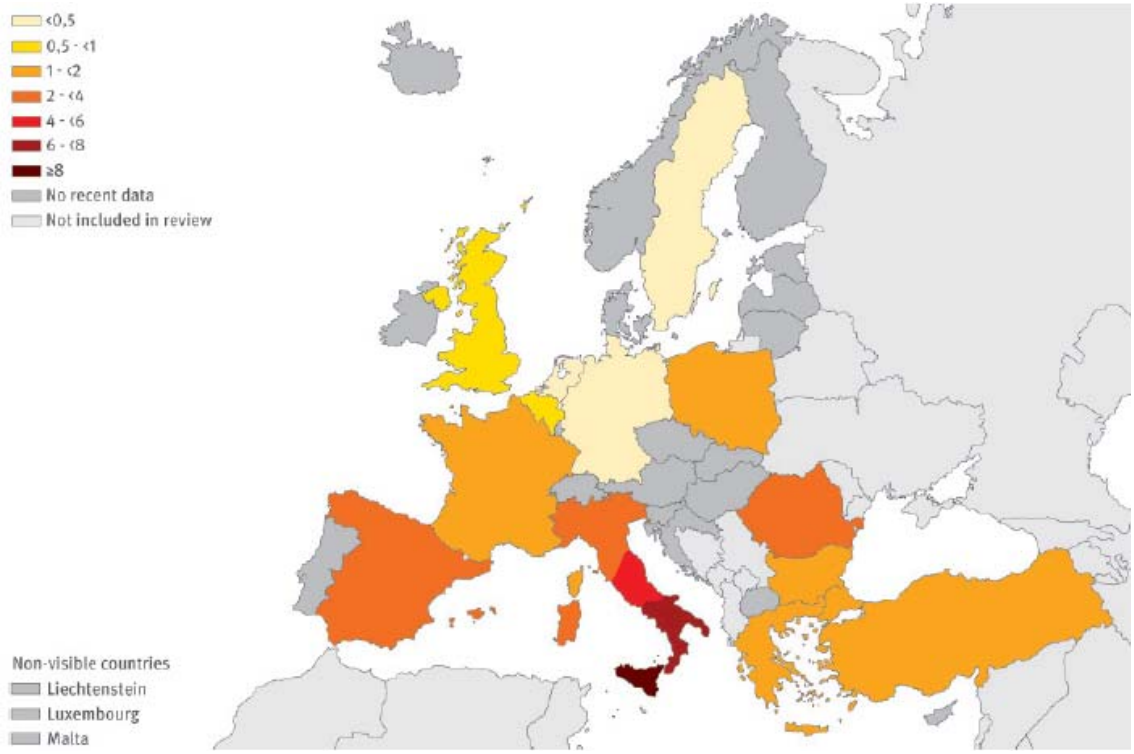
Uncertainty surrounding prevalence estimates is common, even in European countries with a high prevalence of HCV. For example, in one study, Italy was reported to have a high prevalence (3.2%) of HCV, with 1,923,136 infected individuals in 2010[54], whereas another study reported a prevalence rate of 5.2% in the adult population[58]. The incidence rate for the period 1997–2004 was estimated to be 1.03 (95% CI 0.59–1.46) per 100,000 population[53].

Lower prevalence rates are reported for the Netherlands (0.13%)[50] and Finland (0.4%)[51].

Appendix 5 presents published studies related to HCV epidemiology. Publications are listed by country, and present specific data, data sources and year(s) for which data are available.

The ECDC has published a graphical representation of HCV prevalence in the general population in Europe[59].

Figure 4.1. HCV prevalence in the general population in Europe



Abbreviation: HCV=hepatitis C virus.

Regional differences exist also in the distribution of HCV genotypes, as shown by reports on the distribution of HCV cases per genotype per country[50,60,61]. Genotype 1 is predominant in Belgium, France, Germany, Greece, Italy, Ireland, Luxemburg, the Netherlands, Spain, Portugal, and Sweden. Subtype 1a is diffuse in England and Sweden, whereas subtype 1b prevails in France, Germany, Portugal, and Spain. Genotype 3 is reported in 46% and 50% of all HCV cases in Finland and Norway, respectively[50]. Genotypes 2 and 3 prevail in the UK, genotypes 4 and 5 are found mainly in Africa, and genotype 6 mainly in Asia[54].

The ECDC provided estimates of the prevalence of chronic HCV in specific subpopulations **(A0003)** including[59]:

- First-time blood donors: the prevalence ranged from 0.02% to 3.3% in European countries.
- Intravenous drug users (IDUs): the prevalence was 71% in 2002[62]. Intravenous drug use is the most common transmission category with a prevalence of 58.6% among reported

chronic HCV cases. According to a more recent review[63], the prevalence of IDUs in Europe remains high, second only to Africa. The mean prevalence in Europe is 65.9% (95% CI 64.9–66.9%)[47].

- Pregnant women: the prevalence ranged from 0% to 1.7% in European countries.
- Men who have sex with men (MSM): the prevalence was 1.3% in Amsterdam (Netherlands) in 2003[64], and 2.9% in 7 cities in Croatia between 2003 and 2006[65].
- Migrants and minority population: the prevalence ranged widely from 0% to 23.4%. Germany has the largest number of infected migrants.

The prevalence of HCV is lower in younger people than in the older[54,66]**(A0003)**. In 2012, 54% of all HCV cases reported occurred among those aged 25–44 years, whereas only 9.5% of cases occurred among patients < 25 years of age[47].

A male:female ratio of 2 emerged from ECDC surveillance data[47]**(A0003)**. The higher prevalence rate in males could be justified by higher rates of intravenous drug use[60]. A difference in age distribution between male and females was evident in Germany and Greece[50,60]; in France, a higher prevalence was reported in females[60].

[A0002c] What is the mortality rate for HCV and its complications?

HCV caused at least 86,000 deaths in Europe in 2002, 35% of which were associated with cirrhosis, and 32% with liver cancer deaths[53]. At the country level, mortality rates range between 0.1 and 3.5 deaths per 100,000 population.

In women, the mortality rate for cirrhosis ranged from 1.02 per 100,000 population in Malta to 20.91 per 100,000 in Hungary, and in men, from 4.4 per 100,000 population in the Netherlands to 68.27 per 100,000 in Hungary[59].

The 3-, 5-, and 10-year survival rates of compensated cirrhosis were estimated to be 96%, 91%, and 79%, respectively[67]. The probability of survival after diagnosis of decompensated HCV-related cirrhosis was 50.8% at 5 years[68].

A retrospective study[68] identified six variables that significantly predict survival for decompensated HCV-related cirrhosis:

- Age of the patient.
- Baseline Child–Pugh score.
- Type of the first decompensation (ascites, portal hypertensive gastrointestinal bleeding, severe bacterial infection, hepatic encephalopathy).
- Bilirubin level.
- Leucocyte count.
- Presence of more than one decompensation during follow-up.

The ECDC[59] estimated a country level annual mortality rate for hepatocellular cancer (HCC) (Table A168 in Appendix 5) based on data from previous reports[69-71]. The rate of HCC mortality varies widely across European countries, ranging, in women, from 0.27 per 100,000 population in Sweden to 5.35 per 100,000 in Bulgaria.

Analyses of temporal trends in cause-specific mortality among HCV patients in Scotland, New South Wales (Australia), and British Columbia (Canada)[72] show how the individual risk of liver-related death remained largely unchanged during the period 1997–2010. No treatment effect was detectable on population mortality level.

Some of the variation among countries for HCC and cirrhosis may be due to validity of certification.

[A0023] How many people belong to the target population? Specify, if possible, for each genotype.

An estimate of the HCV prevalent population is based on:

- Eurostat data referring to population on 1 January 2015 in each European country.
- Prevalence data from the most recent literature. Variability of data are taken into account providing 95% CI values of prevalence estimates and/or different estimates of prevalence rates are reported in the literature. Key publications were consulted[50,60]; additional reports were used[53] or countries not covered by these publications.

Distribution of prevalent cases per genotype is reported according to available evidence. Estimates are reported in Table 4.1.

Comments on the variability in prevalence and incidence rates among countries are reported in **(A0002)**.

Table 4.1. Estimate of HCV prevalence by country in 2015*

Region/Country	Population (N)	HCV prevalence										Reference(s)
		n (%)	95% CI	Range (n)	Genotype (%)							
					G1	G2	G3	G4	G5	G6	Other	
EU (28 countries)	508,191,116	–	–	–	–	–	–	–	–	–	–	–
EU (27 countries)	503,965,800	–	–	–	–	–	–	–	–	–	–	–
Euro area (19 countries)	338,335,120	–	–	–	–	–	–	–	–	–	–	–
Euro area (18 countries)	335,413,858	–	–	–	–	–	–	–	–	–	–	–
Euro area (17 countries)	–	–	–	–	–	–	–	–	–	–	–	–
Albania	2,893,005	43,395 (1.5)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Andorra (2013)	76,246	–	–	–	–	–	–	–	–	–	–	–
Armenia (2013)	3,026,878	121,075 (4.0)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Austria	8,584,926	42,925 (0.5)	0.1–0.7	8,585–60,094	72.0	5.0	19.0	4.0	–	–	–	Bruggmann 2014[60]
Azerbaijan	9,593,038	383,722 (4.0)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]

Belarus	9,480,868	208,579 (2.2)	1.4–NR	132,732–NR	–	–	–	–	–	–	–	Lavanchy 2011[54]; Mühlberger 2009[53]
Belgium	11,258,434	101,326 (0.9)	0.1–1.1	11,258–123,843	59.0	6.0	19.0	14.0	2.0	–	–	Bruggmann 2014[60]
Bosnia and Herzegovina	3,825,334	57,380 (1.5)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Bulgaria	7,202,198	129,640 (1.8)	1.1–NR	79,224–NR	–	–	–	–	–	–	–	Lavanchy 2011[54]; Mühlberger 2009[53]
Croatia	4,225,316	63,380 (1.5)	1.4–NR	59,154–NR	–	–	–	–	–	–	–	Lavanchy 2011[54]; Mühlberger 2009[53]
Cyprus	847,008	4,235 (0.5)	0.1–NR	847–NR	–	–	–	–	–	–	–	Lavanchy 2011[54]; Mühlberger 2009[53]
Czech Republic	10,538,275	63,230 (0.6)	0.2–0.7	21,077–73,768	66.0	1.0	31.0	2.0	–	–	–	Bruggmann 2014[60]
Denmark	5,659,715	33,958 (0.6)	0.5–0.6	28,299–33,958	46.0	8.0	43.0	3.0	–	–	–	Bruggmann 2014[60]
Estonia	1,313,271	65,664 (5.0)	–	–	–	–	–	–	–	–	–	Lavanchy

												2011[54]
Finland	5,471,753	27,359 (0.5)	0.4–0.6	21,887–32,831	32.0	16.0	46.0	6.0	–	–	–	Saraswat 2015[50]
Former Yugoslav Republic of Macedonia	2,069,172	–	–	–	–	–	–	–	–	–	–	–
France	66,352,469	464,467 (0.7)	0.5–0.8	331,762–530,820	60.0	9.0	20.0	9.0	2.0	0.2	–	Bruggmann 2014[60]
Georgia (2012)	4,497,617	301,340 (6.7)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Germany	81,174,000	405,870 (0.5)	0.5–0.9	405,870–730,566	63.0	6.0	27.0	3.0	–	–	–	Bruggmann 2014[60]
Greece	10,812,467	162,187 (1.5)	0.8–2.1	86,500–227,062	45.0	7.0	34.0	14.0	–	–	–	Saraswat 2015[50]
Hungary	9,849,000	216,678 (2.2)	0.9–NR	88,641–NR	–	–	–	–	–	–	–	Lavanchy 2011[54]; Mühlberger 2009[53]
Iceland	329,100	1,646 (0.5)	0.1–NR	329–NR	–	–	–	–	–	–	–	Lavanchy 2011[54]; Mühlberger 2009[53]
Ireland	4,625,885	41,633 (0.9)	0.6–1.5	27,755–69,388	56.0	4.0	39.0	1.0	–	–	–	Saraswat 2015[50]

Italy	60,795,612	1,945,460 (3.2)	2.6–4.0	1,580,686–2,431,824	62.0	34	–	–	4.0	–		Lavanchy 2011[54]; ECDC 2010[55]; Deuffic–Burban 2012[73]
Kosovo	1,804,944	–	–	–	–	–	–	–	–	–	–	–
Latvia	1,986,096	43,694 (2.2)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Liechtenstein	37,369	–	–	–	–	–	–	–	–	–	–	–
Lithuania	2,921,262	64,268 (2.2)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Luxembourg	562,958	3,941 (0.7)	0.4–0.9	2,252–5,067	55.0	4.0	34.0	6.0	–	–	–	Saraswat 2015[50]
Malta	429,344	4,293 (1.0)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Moldova	3,555,159	81,769 (2.3)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Monaco (2005)	33,085	NR	–	–	–	–	–	–	–	–	–	–
Montenegro	622,099	–	–	–	–	–	–	–	–	–	–	–
Netherlands	16,900,726	30,421 (0.2)	0.1–0.3	10,140–50,702	49.0	10.0	29.0	11.0	–	–	1.0	Saraswat 2015[50]
Norway	5,165,802	30,995 (0.6)	0.5–0.7	25,829–36,161	40.0	9.0	50.0	1.0	–	–	–	Saraswat

												2015[50]
Poland	38,005,614	304,045 (0.8)	0.5–1.0	190,028–380,056	79.0	0.0	14.0	5.0	–	–	2.0	Saraswat 2015[50]
Portugal	10,374,822	155,622 (1.5)	1.2–1.9	124,498–197,122	58.0	2.0	28.0	9.0	0.2	–	3.0	Bruggmann 2014[60]
Romania	19,861,408	893,763 (4.5)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]; Mühlberger 2009[53]
Russia	146,267,288	5,996,959 (4.1)	3.5–4.6	5,119,355–6,728,295	55.0	8.0	36.0	–	–	–	–	Saraswat 2015[50]
San Marino	32,789	–	–	–	–	–	–	–	–	–	–	–
Serbia	7,111,973	106,680 (1.5)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Slovakia	5,421,349	65,056 (1.2)	0.7–1.6	37,949–86,742	90.0	2.0	7.0	1.0	–	1.0	1.0	Saraswat 2015[50]
Slovenia	2,062,874	20,629 (1.0)	–	–	–	–	–	–	–	–	–	Lavanchy 2011[54]
Spain	46,439,864	696,598 (1.5)	1.1–1.9	510,839–882,357	69.0	3.0	20.0	8.0	–	–	–	Bruggmann 2014[60]
Sweden	9,747,355	58,484 (0.6)	0.5–0.7	48,737–68,231	50.0	20.0	30.0	–	–	–	–	Bruggmann 2014[60]
Switzerland	8,236,573	131,785 (1.6)	0.8–1.8	65,893–148,258	52.0	9.0	29.0	10.0	–	–	–	Bruggmann 2014[60]

Turkey	77,695,904	699,263 (0.9)	0.7–1.1	543,871–854,655	92.0	2.0	5.0	1.0	–	–	–	Bruggmann 2014[60]
UK	64,767,115	259,068 (0.4)	0.3–0.6	194,301–388,603	44.0	5.0	47.0	4.0	–	–	–	Bruggmann 2014[60] Public Health England 2014[74]
Ukraine (2013)	45,372,692	1,814,908 (4.0)	1.2–NR	544,472–NR	–	–	–	–	–	–	–	Lavanchy 2011[54] Mühlberger 2009[53]

*Unless otherwise indicated in column 1.
Abbreviations: CI=confidence interval; ECDC=European Centre for Disease Prevention and Control; HCV=hepatitis C virus; n=number of subjects; NR=not reported.

[A0003a] What are the known risk factors for chronic hepatitis C?

The transmission of HCV occurs primarily through exposure to infected blood. Risks for transmission include[54,66,75]:

- Iatrogenic routes, such as blood transfusion, haemodialysis, solid organ transplantation from an infected donor, or injections for medications and immunisations. Transmission is possible when syringes, needles, or other medical equipment are reused from patient to patient without sterilisation. In developed countries, the introduction of screening assays reduced this risk to less than 1 per 1,000,000 units of blood, and, since the 1990s, the transmission of HCV via other blood products and organ transplantation has been reduced to zero[76]. European countries are experiencing the long-term effects of the past transfusion-associated HCV epidemic because of the natural history of HCV **(A0004)**.
- Intravenous drug use and injections applied outside of medical settings. There is a wide variation in the prevalence of HCV among IDUs in the EU. A prevalence rate of 60% is common, while a rate < 40% has been reported in some regions of Belgium, Greece, the UK, Austria, the Czech Republic, Cyprus, Finland, Hungary, Malta, the Netherlands, and Slovenia[75]. The factors associated with an increased risk of HCV in IDUs are age, duration and frequency of intravenous drug use, sharing equipment, polydrug use, homelessness, and having served a prison sentence[75].
- High-risk sexual activity. Although high-risk sexual activity isn't a major driver of the HCV epidemic, HCV has become a problem in HIV-positive men who have sex with men (MSM), with a reported incidence of 4.09 per 100 person-years (95% CI 2.57–6.18) in a Swiss HIV cohort[77]. Risk factors predisposing to HCV infection are a history of inconsistent condom use, past syphilis, and unprotected anal intercourse with multiple partners[76,78].
- Occupational exposure.
- Household exposure/contacts[66,79].
- Birth to an infected mother. Even if vertical transmission is rare, birth to an infected mother is the first cause of HCV infection among children even in Europe[76]. The average risk is about 4% per birth with approximately one-third of transmissions occurring in utero.
- Intranasal drug use. Intranasal transmission of HCV via contaminated shared drug-sniffing implements is a potential source of viral infection. Blood and HCV particles can be transferred onto sniffing implements (e.g. straws).
- Tattooing, acupuncture, body piercing, scarification techniques, cosmetic procedures, and commercial barbering.

The risk factors for developing chronic HCV infection are:

- Age at the time of infection. The chronicity rate in HCV appears to be lower in younger individuals[66], the role of age in the chronicity rate of HCV infection isn't clear in literature. Age might facilitate viral clearance and/or strength of immune response and/or be associated with slowly progressive disease. In a study conducted in Italy[80] residents aged12–25 years had a chronicity rate of 56%, compared with 87% for those > 25 years of age.
- No jaundice or symptoms during acute infection. The rate of chronic HCV infection is lower in patients who develop jaundice or symptoms[66].
- Ethnicity. The rates of chronic HCV infection vary between different racial and ethnic groups. African Americans appear to have a higher rate of chronic HCV infection than Caucasians and Hispanic whites[66]. In light of this, the impact of immigration on HCV prevalence at European level is a sensitive topic[75], especially when immigrants come from countries traditionally characterised by a high rate of endemicity[76].
- HIV infection.
- Immunosuppression.

No consistent data are available on the association between chronic HCV and gender. The chronicity rate of HCV appears to be lower in women, with retrospective analyses conducted in pregnant women

reporting a chronicity rate of 55%[66]. However, large cross-sectional studies did not find any difference between genders[66,80].

[A0003b] What are the known risk factors for progression of liver fibrosis?

The risk factors for progression of liver fibrosis in HCV patients are:

- Alcohol consumption. A major cause of liver cirrhosis is heavy alcohol consumption, particularly in females[54]. The interaction between lifetime daily alcohol intake and HCV is additive for consumption between 50 and 125 g/day and multiplicative for consumption above 125 g/day[61]. The median rate of fibrosis progression per year increased from 0.125 to 0.167 in patients whose alcohol consumption was ≥ 50 g/day[81]. Bellentani[79] reported that an alcohol consumption > 30 g/day significantly aggravates the natural course of HCV.
- Age. In children, hepatitis C has a less aggressive course, with a low rate of fibrosis formation compared to adults infected for the same length of time[82], as a result of fewer comorbidities such as alcohol consumption, haemochromatosis, and non-alcoholic fatty liver disease. Even though a significant association between the rate of fibrosis progression and the age at the moment of infection wasn't found, Poynard et al. found that the rate of fibrosis was 31% higher in patients aged 31–40 years compared to those aged 21–40 years[81]. After adjustment for estimated duration of infection, the grade for stage of fibrosis was significantly higher in patients infected at 40 years or older than in younger patients.
- Duration of the infection. A longer duration is associated with a higher grade of liver fibrosis[41].
- HCV coinfections with HIV or hepatitis B virus (HBV). HIV seropositivity and low CD4 count appear to accelerate HCV liver fibrosis[66]. Conversely, HCV has been associated with a faster progression of HIV to acquired immunodeficiency syndrome (AIDS).
- Serum levels of alanine aminotransferase (ALT) during chronic hepatitis C. Higher levels of ALT are associated with an increased risk of liver fibrosis progression. Normal liver enzymes do not exclude the possibility of fibrosis progression[66].

On the other hand coffee consumption is a protective factor. High levels of coffee consumption reduce serum levels of ALT and γ-glutamyl transferase, whose reduction is associated with milder fibrosis[83].

[A0003c] What are the known risk factors for decompensated cirrhosis?

The risk factors for decompensated cirrhosis in HCV patients are:

- HCV coinfections with HIV. Patients have faster progression to decompensated liver disease[83].
- Intravenous drug use. The number of existing infected IDUs progressing towards advanced stages of cirrhosis is rapidly increasing, reflecting the advancing age of those individuals[84].
- High levels of alcohol consumption, particularly above 350 g/week. A total of 24% of the entire HCV-diagnosed population (27% of HCV-diagnosed IDUs) experienced an alcohol-related admission; this proportion increased to 50% of all patients, and to 63% of the current/former IDUs who developed decompensated cirrhosis[84].
- Genotype. From an observational cohort study emerged that HCV infected patients with genotype 3 have a higher risk of developing decompensated cirrhosis respect to patients with genotype 1 (HR 1.42, 95% CI 1.32-1.52)[85].

[A0003d] What are the known risk factors for hepatocellular carcinoma?

The risk factors for hepatocellular carcinoma (HCC) in HCV patients are[41,83]:

- Liver cirrhosis. HCC can often be the first clinical complication of HCV-related liver cirrhosis before hepatic decompensations become evident.
- Age.
- Male gender.

- Genetic factors. A genome-wide association study in 721 individuals with HCV-related HCC shows that a single nucleotide polymorphism (SNP) (rs2596542) at the gene encoding for MICA (MHC [major histocompatibility complex] class I chain-related A) was strongly associated with the onset of HCC in HCV-infected individuals[86].
- Genotype. From an observational cohort study emerged that HCV infected patients with genotype 3 have a higher risk of developing hepatocellular carcinoma respect to patients with genotype 1 (HR 1.63, 95% CI 1.47-1.79)[85].
- HCV coinfections with HIV. Patients have faster progression to HCC, especially during immunosuppression, while antiretroviral therapy might reduce the risk for HCC.
- HCV coinfections with HIV.
- HCV coinfections with HBV.
- Type 2 diabetes.
- Insulin resistance.
- Cigarette smoking.
- Alcohol consumption. A study on the dose–effect relationship between alcohol drinking and HCC in HCV patients in Italy reported that the risk of HCC increased with increasing level of alcohol intake, irrespective of duration of consumption and age at start, both in women and men[87].
- Coffee consumption. Studies have suggested an inverse association between coffee drinking and risk of HCC.
- Obesity.

No consistent data are available on the association between HCC risk and:

- HCV genotype. A meta-analysis of 21 studies reported that patients with HCV genotype 1b infection had an almost 2-fold greater risk of developing HCC (1.78; 95% CI 1.36–2.32) than patients with other HCV genotypes[88]. The same study reported a lower pooled risk (1.60; 95% CI 1.07–2.39) by restricting the analysis to 8 studies only on patients with liver cirrhosis. While extending the analysis to all 36 available studies, without adjusting data, the pooled risk reached 2.46 (95% CI 1.69–3.59).
- HCV load or quasispecies[83].

Furthermore, it has been shown that there are synergistic interactions between different risk factors[41].

[A0004] What is the natural course of the condition?

The natural course of HCV infection is represented in a diagram in Figure 4.2.

HCV is acquired mainly through contact with infected blood. Blood-to-blood contact can happen through transfusion of infected blood or blood components, or when sharing needles (e.g. for drug injection, tattooing, or piercing), razors, straws for drug inhalation, etc. Accidental contact is possible in the case of healthcare workers. Less common modes include sexual and perinatal transmission. **(A0003)**.

Virus replication starts early and viraemia (measured as level of HCV RNA) rises rapidly during the first few weeks; it is possible to detect HCV RNA in serum 7–21 days after the exposure[42,89-92] with peaks between 10^5 to 10^7 IU/mL preceding the peak of serum ALT and bilirubin and the accompanying onset of symptoms[66,93].

The latent period, i.e. the time from acquisition of the infection to the first ALT elevation considered compatible with the onset of hepatitis, lasts 30 days to 8 weeks[42,89]. ALT concentration can reach values greater than ten times the baseline level, while serum bilirubin can be increased to ≥ 2 times the baseline level[93]. The viral strain and the amount of the inoculum influence the course of acute hepatitis C only very modestly, with longer latent periods associated with non-1 HCV genotypes and transmission of only small amounts of viral loads[42].

Almost all patients develop antibodies to HCV (anti-HCV), which can be detected in serum by enzyme immunoassay 1–3 months (mean 36 days) after exposure[66,90,93,94]. Immunocompromised patients may experience prolonged periods of up to 12–48 weeks before seroconversion can occur[41], and titres might be low or undetectable[66]. According to one report, anti-HCV antibodies persist during all stages of the infection and for up to 9 years after clearance of acute HCV infection[90].

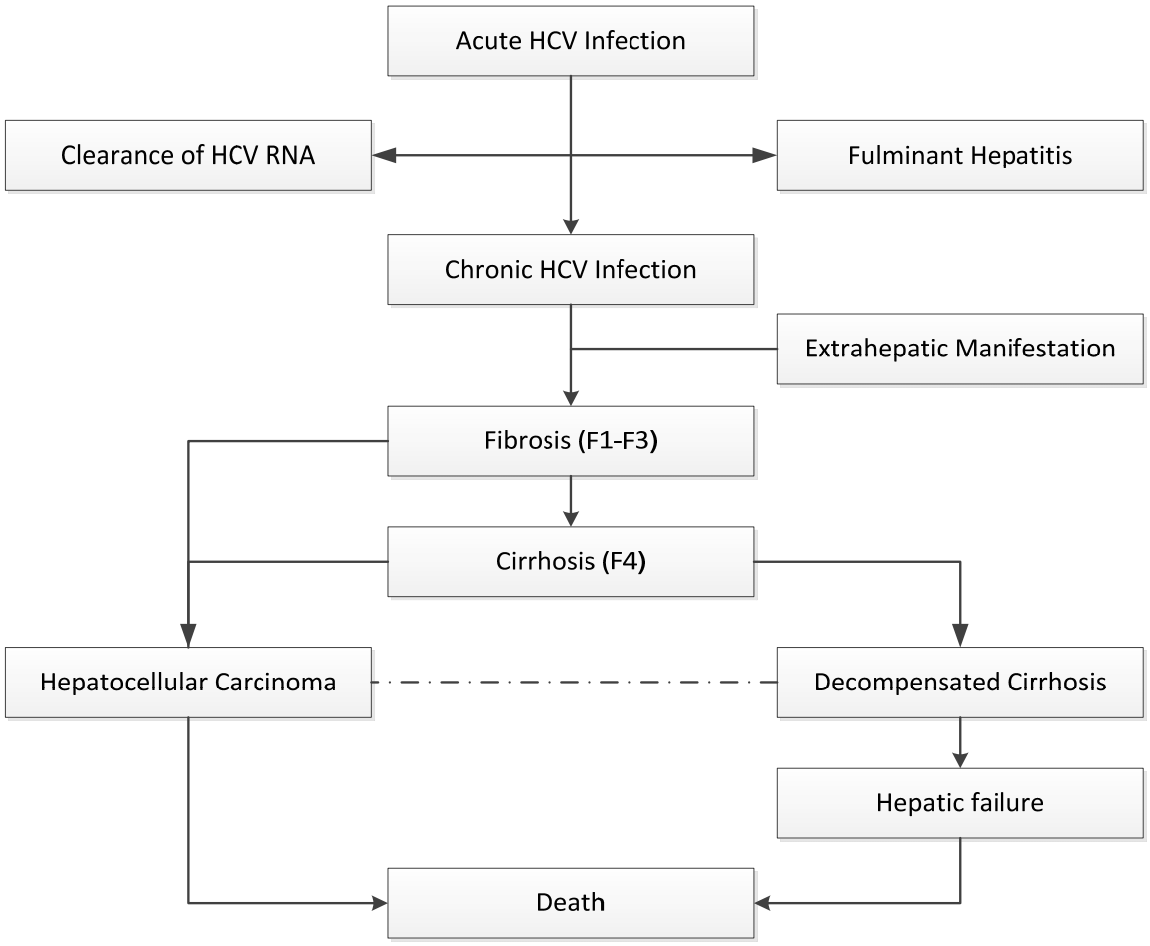
During the initial acute phase of the infection, the majority of patients are asymptomatic; consequently, acute hepatitis C infection is frequently undiagnosed. Some (20–30%) patients[66] develop mild clinical symptoms 3–20 weeks (mean 7 weeks) after viral transmission[91]. Reported symptoms include fatigue, nausea, abdominal pain, loss of appetite, mild fever, itching or myalgia; 50–84% of clinically overt patients with acute HCV infection develop jaundice, however, most clinical signs are non-specific[41] **(A0005)**.

Fulminant hepatic failure associated with acute courses of hepatitis C has been reported in rare cases[95].

The frequency of spontaneous viral clearance ranges widely in published studies, from 0% to 80%. The difference in estimates is due to variability in the study in terms of population (age, gender, country), sample size, and time of assessment. A systematic review conducted on longitudinal studies estimated a weighted mean clearance rate of 26%[96].

The majority of cases of spontaneous viral clearance occur by 6 months. Comparing 6 and 12 month rates (73-86% vs. 87-95%), spontaneous clearance appears less common after 6 months[94].

Figure 4.2. Natural history of HCV



Abbreviations: F=fibrosis stage; HCV=hepatitis C virus; RNA=ribonucleic acid.

Chronic HCV infection is defined by the persistence of HCV infection for at least 6 months, diagnosed by the detection of HCV RNA in serum[97]. Chronic hepatitis C can cause fibrosis, a continuous

structural liver damage process in which chronic inflammation stimulates production and accumulation of collagen and extracellular matrix proteins. In mild cases, fibrosis is limited to the portal and periportal areas of the liver. Fibrosis extended from one portal area to another is known as 'bridging fibrosis'[66].

Fibrosis can potentially progress into liver cirrhosis within 20 years in 5–10% of individuals[98], with a variable annual rate of 0–8%[99-101]. Cirrhosis is defined as "a diffuse process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules"[102].

Liver biopsies are the gold standard for assessing hepatitis C in terms of grade and stage. The grade defines the extent of necrotic and inflammatory activity caused by the disease; it is gauged by the amount of mononuclear inflammatory cells, and dead or dying hepatocytes found. The stage establishes the extent of the structural liver damage or fibrosis, or the presence of cirrhosis[66,103]. Various scoring systems have been developed for the histological assessment (Table A169 in Appendix 5), the most common being the French METAVIR, the Batts-Ludwig, the International Association for the Study of the Liver (IASL), and the Ishak Scoring systems[103].

Patients with chronic hepatitis C may report symptoms such as right abdominal discomfort, nausea, fatigue, myalgia, or arthralgia, and present with signs of weight loss **(A0005)**. However, all of these clinical features are non-specific and cannot be associated with the severity of liver injury, as the progression of cirrhosis is often clinically silent.

HCC has been confirmed to be the prevalent complication and primary cause of death in patients with HCV-related cirrhosis. At the same time, HCV is one of many cofactors or risk factors for HCC **(A0003)**. The incidence of HCC is 20–30 times greater in HCV-infected patients than in the uninfected population[84,104], and at least one third of HCC cases can be attributed to HCV infection[40,41]. HCC can be the first clinical finding of HCV-related liver cirrhosis before hepatic decompensations become evident[105]. Decompensated cirrhosis occurs at an annual incidence of 3.9%[68], and has a poor prognosis, with a 5-year survival rate of 50%[68]. It is characterised by[66,68]:

- Ascites.
- Upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy.
- Severe bacterial infection.
- Hepatorenal syndrome.
- Hepatic encephalopathy.

Chronic hepatitis C is also responsible for extrahepatic manifestations (EHMs) involving renal, dermatological, haematological, and rheumatological systems. At least one clinical EHM develops in 74% of patients with HCV infection[106]. EHMs might be the leading clinical manifestation of HCV infection and can determine the overall prognosis of the disease **(A0005)**.

The most common and documented EHM is mixed cryoglobulinaemia (MC)[106,107], which can be found in 19% to > 50% of HCV-infected individuals[107]. MC is characterised by the presence of circulating cryoglobulins, which are immunocomplexes produced by a B-cell lymphoproliferative disorder that deposited in vessels. Approximately 10–30% of the patients with detectable cryoglobulins develop clinical signs[66,107], further specified in **(A0005)**.

Chronic HCV infection has been also associated with an increased risk of immunoproliferative malignancies, B-cell non-Hodgkin lymphoma, multiple myeloma, and cancers of the pancreas, rectum, kidney, and lung[104,108-110].

Following treatment, patients with cirrhosis who achieve a sustained viral response (SVR) are at risk for hepatic decompensation, HCC, and death in the short term (5 years)[103,111].

Increasing attention has been paid to a new entity, known as occult HCV infection (OCI), which was first described in 2004[112], and which may be responsible for recurrent disease weeks to years after the achievement of an apparent SVR. OCI is defined as the presence of genomic HCV RNA in liver tissue, peripheral blood mononuclear cells (PBMCs), and/or concentrated plasma triglyceride-rich

factions, in the absence of detectable levels of HCV RNA in serum, and in the absence or presence of anti-HCV antibodies[113,114]. According to Attar[113], there are currently two immune-viral/clinically distinct forms of OCI:

1. "Detectable HCV-RNA and anti-HCV, in the absence of elevated liver enzymes, which occurs in otherwise successful antiviral therapy or a self-limiting episode of hepatitis C. These individuals have HCV RNA detected in their serum, PBMCs, and liver. And have been labelled as having "secondary OCI" indicating the presence of residual HCV infection persisting despite spontaneous resolution of hepatitis C or achieving apparent "SVR" following HCV therapy" as described by Pham[112].

2. "Individuals presenting with HCV-RNA positivity but anti-HCV negative with elevated liver enzymes" as described by Castillo[115].

The natural history of OCI is not yet fully understood[113].

Effects of the disease or health condition

[A0005] What are the symptoms and the burden of disease for the patient?

Chronic hepatitis C is generally asymptomatic; however, infected patients may present non-specific, mild, vague, and intermittent symptoms. Even though these are rarely incapacitating, they can reduce extensively the quality of life. Reduced health-related quality of life has been associated with HCV infection, independent of the stage of liver disease[116].

The percentage of patients who develop symptoms has not been determined exactly, since individuals who present to a physician for diagnosis and management are usually those with a symptomatic condition.

The most frequent symptom referred to by patients is fatigue, which has been reported to develop in about 20–80% of individuals with chronic HCV infection[41]. Other symptoms, not as frequent as fatigue, are[41,91,117]:

- Nausea.
- Poor appetite.
- Myalgias.
- Arthralgias.
- Feverishness.
- Weight loss.
- Right upper quadrant pain.
- Dark urine.
- Itching.
- Fluid retention.
- Easy bruising.

Chronic HCV infection may also cause EHMs in 40–70% of patients; the disorder with the strongest link to HCV infection is MC[41], an immune-complex-mediated systemic vasculitis[118]. MC is asymptomatic in most patients, but 3–30% of patients develop related symptoms (MC syndrome)[41], which vary from subject to subject. The main clinical manifestations of MC include[118,119]:

- Cutaneous lesions and vasomotor symptoms: purpura, leg ulcers, Raynaud's phenomenon, livedo, and urticaria.

- Rheumatological manifestations: arthralgias and myalgias.
- Peripheral neuropathy.
- Sicca syndrome: xerostomia and xerophthalmia.
- Gastrointestinal bleeding and abdominal pain.
- Renal manifestations.
- Myocardial infarction.

In general, the presence of symptoms in HCV infection is independent from the activity, severity, and prognosis of the disease, although symptoms seem to be more common once cirrhosis develops[91]. Often, individuals with the infection become aware of their condition only when severe liver disease is present.

With cirrhosis, symptoms and signs appear along with those of end-stage liver disease, including:

- Jaundice.
- Weakness.
- Wasting syndrome.
- Gastrointestinal bleeding.

Chronic hepatitis C is also a major cause of HCC, especially in patients with advanced disease[91], as presented in **(A0002, A0004)**.

It has been also suggested that chronic HCV infection might be associated with a modest but significantly increased risk of developing type 2 diabetes[120].

It has been observed that patients with HCV infection may also have central nervous system involvement, as some of them show evidence of neurophysiological disturbance and cerebral metabolite disturbance[121]. This could be related to the development of cognitive impairment diagnosis and symptoms, as well as feelings of fear, denial, anger, depression, anxiety, and sadness that patients describe. Many patients also experience concern about an onward transmission to their partners and, in the case of women, to their children too, a fact that affects their family lives. Patients have referred to an 'internalised stigma' related to the involvement of an infectious agent, as well as stigmatising attitudes towards them from family, friends, colleagues, and even within the healthcare setting, because of the association of HCV with injecting illegal drugs and HIV/AIDS[116].

What is the rate of mortality and/or hospitalisation caused by the disease?

Chronic HCV infection is associated with increased morbidity and both liver-related mortality and overall mortality, as reported in **(A0002)**.

HCV-associated hospital admissions have been analysed from population-based registers. All-cause hospitalisation rates for HCV-monoinfected patients are 42% higher than rates for the general population, with peaks among those aged 15–64 years, and the greatest excess among those aged 15–19 years[122]. During a 3-year follow-up period of 191 patients with chronic HCV infection in the US, nearly all individuals were hospitalised with different diagnoses: HCV infection as a primary diagnosis accounted for 22% (38/175) of all hospitalisations, and the mean length of stay (LOS) was 11 days; cirrhosis-related admissions accounted for 20 (out of 175) hospitalizations, with a mean LOS of 6 days; another 6 hospitalisations were caused by 'other liver diagnoses', with a mean LOS of 31 days[123].

All-cause and liver-related hospitalisations in patients with chronic HCV increase every year, presenting annual growth rates of 11–28% and 13–23%, respectively[84,124-126]. LOS also increases every year with growth rates of 22–24% for all-cause admissions, and 17–20% for liver-related cases[124,125].

An accelerated natural history of hepatitis C is observed in patients aged 40–59 years and in HIV/HCV-coinfected patients, with average annual growth rates (of both all-cause hospitalisation and LOS) varying from 17% to 42%[84,124,125] and 30% to 40%, respectively[125].

Hepatitis C is the principal cause of death from liver disease **(A0002)**. Liver-related death is caused either by HCC or hepatic decompensation, and HCV-infected patients have an increased risk of liver-related death compared with the general population[109]. As observed by Planas[68] after the first significant hepatic decompensation, the probability of survival is 81.8% at 1 year, and 50.8% at 5 years. The only treatment option for those patients who have developed decompensated cirrhosis is a liver transplant; HCV has become the most commonly reported primary indication for liver transplant in many industrialised countries.

[A0006] What is the burden of the disease for society?

The burden of chronic HCV is associated with its long-term consequences of liver cirrhosis, HCC, and liver transplantation as described in **(A0004)**.

The incidence, prevalence, and mortality rates of HCV are reported in **(A0002)**.

Multiple studies have estimated medical resource use and HCV-related costs in European countries[127-131]. Only two studies[128,131] included the costs of new direct-acting antivirals (DAAs) in the burden estimates.

The average total costs in Germany were estimated to be €19,147 per patient based on data available for 315 patients treated in the period 2008–2011[130]. Total costs ranged from €15,749 to €20,182, depending on the severity of HCV. The dominant factor was the cost of antiviral treatment with pegylated interferon (Peg-IFN) plus ribavirin (79.6–84.2%). Total cost for patients with decompensated cirrhosis is €15,749 the majority (72%) of which is accounted for by inpatient care.

In Belgium, data collected on 157 patients in the period 2005–2007, estimated the mean total cost per patient to be €22,373 considering all HCV stages (ranging from mild to HCC)[129]. Compared with the cost for mild disease (€18,993), the cost increased 1.6 times in the case of decompensated cirrhosis (€29,759), 1.9 times in the case of HCC (€35,987), and 3.4 times in the case of liver transplant (€65,120). Hospitalisations were mainly due to ascites (20%) in patients with decompensated cirrhosis, and because of chemoembolisation in the case of HCC. A total of 64% of patients were treated with an antiviral with a higher cost in patients with mild (€13,408) and moderate (€14,767) disease.

Stärkel[132] reported HCV-associated costs projected until 2030 for the Belgian context based on historical data[60]. The total annual burden will peak in 2026 reaching €126 million (95% CI 30–257); in 2014, HCV accounted for €80 million (95% CI 22–181). Decompensated cirrhosis and HCC are expected to increase until 2031 and 2034, respectively, reaching annually €14 and €8 million as shown in Figure 3.3[133]. The later peak for HCC is thought to be due to the long-lasting and age-dependent process of HCC and given that in Europe and the US the majority of infection occurred in the 1970s and 1980s[41]. A further discussion on evolution of HCV burden of disease in Belgium is reported[134].

Figure 4.3. Projected cost of HCV burden of disease in Belgium (1950–2030)

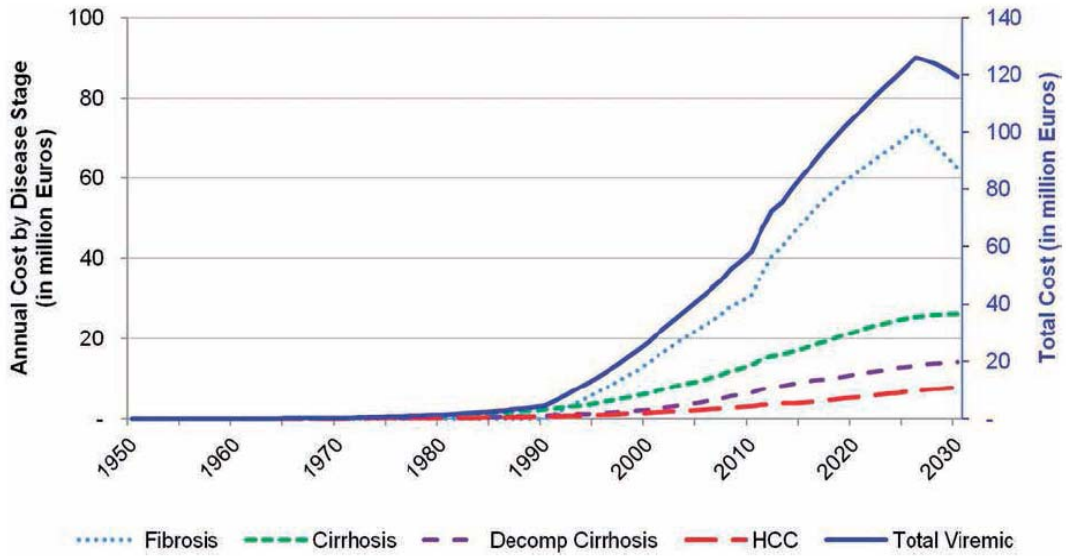


Fig. 3. — Projected HCV sequelae cost : Belgium, 1950-2030

Abbreviations: HCC=hepatocellular cancer; HCV=hepatitis C virus.

The most recent Italian study estimated a total economic burden associated with HCV of €1.06 billion[127]. The cost per patient attributed to HCC ranged from €4,827 to €6,786 per year. The cost of transplantation was estimated to be €90,162 for the surgery and €5,800 for the therapy during the first year after surgery. According to the epidemiological and economical model, the annual burden reached:

- €0.26 billion (95% CI 0.14–0.41) for chronic HCV.
- €0.56 billion (95% CI 0.30–0.89) for cirrhosis.
- €0.051 billion (95% CI 0.0007–0.25) for HCC.
- €0.05 billion (95% CI 0.03–0.08) for liver transplantation.
- €0.15 billion (95% CI 0.07–0.27) because of HCV-induced deaths.

The Italian model showed that indirect costs exceed €643.03 million (95% CI 369.25–991.51) which correspond approximately to 60.6% of total yearly costs; out-of-pocket costs were not estimated[127].

For Italy, an extrapolation of HCV costs until 2030 was conducted using a system dynamic model[128]. Assuming 1.2 million infected subjects in 2012, 211,000 patients diagnosed, and 11,800 being treated with anti-HCV drugs, the spending peak of direct health care costs was estimated in 2012 and equal to about €527 million. In the following years the model predicted a cost reduction until 2030 (last year of analysis).
Scenario analysis was conducted to take into account the introduction of new, more effective treatments that are able to reduce HCV prevalence. A strongly conservative assumption made in all scenarios was that the cost of the new treatment is comparable to the cost of protease inhibitor therapy.

In Switzerland, the annual healthcare cost of viraemic HCV (excluding antiviral treatment costs) was estimated at €74 million (95% CI 36–157) in 2013[131]. The number of advanced stage cases was projected to increase until 2030[131], at which point the annual economic burden of untreated viraemic infections was estimated at €96.8 million (95% CI 36–232). Scenarios were considered to take into account the effects of policies able to reduce HCV liver-related mortality. To reduce mortality by 90% by 2030, it would be necessary to treat 4,190 ≥ F2 or 3,200 ≥ F3 patients annually by 2018, using

antivirals with a 95% efficacy rate. A 2- and 5-year delay in the ≥ F2 strategies was expected to lead to 80% and 300% more liver-related deaths in years 2030, respectively.

In France and Romania[135] the total current burden was estimated being €22 billion and €5 billion, respectively. These estimates didn't considered new DAAs. Cost of treatments of decompensated cirrhosis and liver cancer accounts for 60% - 80% of the total health care costs. It's confirmed that indirect costs represent the largest proportion of the total HCV burden. A projection of costs till 2040 is provided. Despite the fall in HCV prevalence, the increase in the number of patients reaching the later stages is associated with a significant increase in total costs. The increase is lower in the case more efficacious treatments are prescribed.

Current clinical management of the disease or health condition

[A0024] How is the health condition currently diagnosed according to published European guidelines and in practice?

Infection with HCV is diagnosed by testing for specific antibodies using enzyme-linked immunosorbent assay (ELISA)[136].

EASL Recommendations on Treatment of Hepatitis C 2015[34] recommend the assay for anti-HCV antibodies as the first-line diagnostic test for HCV infection. If detected, HCV RNA should be determined by a sensitive molecular method. The presence of HCV does not indicate whether the infection is acute, chronic, or has resolved[136]. To confirm true convalescence anti-HCV-positive, HCV-RNA-negative individuals should be retested 3 months later[34].

HCV-RNA testing should also be performed in persons with a negative anti-HCV test who are immunocompromised (e.g. those receiving chronic haemodialysis) or who might have been exposed to HCV in the preceding 6 months[33].

Given that not all patients with acute hepatitis C will be anti-HCV-positive at diagnosis, attention has to be paid to clinical signs and symptoms compatible with acute hepatitis C (e.g. ALT >10 times the upper limit of normal; jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable.

Prior to therapy, it is necessary to assess:

- Liver disease severity. Identifying patients with cirrhosis or advanced (bridging) fibrosis is of particular importance, as the post-treatment prognosis depends on the stage of fibrosis[34]. Fibrosis stage can be assessed by non-invasive methods initially. The combination of blood biomarkers or the combination of liver stiffness measurement and a blood test improve accuracy. Therefore, liver biopsy could be reserved for cases where there is uncertainty[34]. Histology may be required in cases of known or suspected mixed aetiologies (e.g. HCV infection with HBV infection, metabolic syndrome, alcoholism, or autoimmunity)[34].

- The HCV genotype and genotype 1 subtype (1a/1b), while IL28B genotyping has lost predictive value with the new IFN-free treatment regimens.

Screening for HCV infection is recommended in targeted populations at high risk[34,38]. Rapid diagnostic tests can be used instead of classical enzyme immunoassays to facilitate anti-HCV antibody screening and improve access to care. A sensitive molecular method is requested to identify patients with an ongoing infection.

The AASLD-IDSA 2015 guidelines recommend[33]:

- A one-time HCV test in asymptomatic persons in the 1945–1965 birth cohort and other persons based on exposures, behaviours, and conditions that increase the risk for HCV infection.

- Annual HCV testing for persons who inject drugs and for HIV-seropositive MSM.

- Periodic testing to be offered to other persons at ongoing risk of HCV exposure.

A list of HCV infection risk groups is available[136], however, it is important to remember that risk factors vary from country to country, and the HCV infection risk in various groups. The Canadian Association for Study of the Liver recommends specific tests for each high-risk group to be performed as part of the routine assessment for HCV[137].

[A0025] How is the disease or health condition currently managed according to published European guidelines and in practice?

International, European and national HCV guidelines are available. Please see in Appendix 1 for a list of the different treatment guidelines and HCV drugs covered by them. The EASL recommendations[34] identify as the primary goal of chronic HCV therapy the cure of the HCV infection to prevent the complications of HCV-related liver and extrahepatic diseases, including hepatic necro-inflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe EHMs, and death.

The EASL recommendations[34] select the endpoint of therapy as undetectable HCV RNA in a sensitive assay (≤ 15 IU/mL) 12 weeks (SVR12) and 24 weeks (SVR24) after the end of treatment.

Treatment with Peg-IFN-α plus ribavirin is contraindicated in patients with:

- Uncontrolled depression, psychosis, or epilepsy.
- Pregnant women or couples unwilling to comply with adequate contraception.
- Severe concurrent medical diseases and comorbidities including retinal disease and autoimmune thyroid disease.
- Decompensated liver disease.

The combination of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir in patients with Child–Pugh grade C (decompensated cirrhosis) is contraindicated.

The risk-benefit profile of sofosbuvir in patients with severe renal impairment is still being investigated, The EASL recommendations request that all treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy[34]. EASL prioritisation criteria are reported in Table 4.2.[34].

Table 4.2. EASL prioritisation criteria for the treatment of HCV

Treatment priority	Patient group
Treatment is indicated	All treatment-naive and treatment-experienced patients with compensated and decompensated liver disease
Treatment should be prioritized	Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis
	Patients with HIV coinfection
	Patients with HBV coinfection
	Patients with an indication for liver transplant
	Patients with HCV recurrence after liver transplant
	Patients with clinically significant extrahepatic manifestations
	Patients with debilitating fatigue
	Individuals at risk of transmitting HCV (active intravenous drug users, MSM with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
Treatment is justified	Patients with moderate fibrosis (F2)
Treatment can be deferred	Patients with no or mild disease (F0–F1) and none of the above-mentioned extrahepatic manifestations
Treatment is not recommended	Patients with limited life expectancy due to non-liver-related comorbidities

Abbreviations: EASL=European Association for the Study of the Liver; F=fibrosis stage; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; MSM=men who have sex with men.

The EASL treatment recommendations for HCV-monoinfected or HCV/HIV-coinfected patients depending on diagnosis are reported in Tables 4.3. to 4.5.

Table 4.3. EASL recommended treatment for HCV-monoinfected or HCV/HIV-coinfected patients with chronic hepatitis C without cirrhosis

Genotype	Treatment regimen							
	PR + SOF	PR + SMV	SOF + R	SOF + LDV	OBV/PTV/ r + DSV	OBV/PTV/r	SOF + SMV	SOF + DCV
1a	12 wk	12 wk, then PR 12 wk (treatment-naive or relapsers) or 36 wk (partial or null responders)	No	8–12 wk, without R	12 wk with R	No	12 wk without R	12 wk without R
1b	12 wk		No		12 wk without R	No		
2	12 wk	No	12 wk	No	No	No	No	12 wk without R
3	12 wk	No	24 wk	No	No	No	No	12 wk without R
4	12 wk	12 wk, then Peg-IFN-α and R 12 wk (treatment-naive or relapsers) or 36 wk (partial or null responders)	No	12 wk without R	No	12 wk with R	12 wk without R	12 wk without R
5 or 6	12 wk	No	No	12 wk without R	No	No	No	12 wk without R

Abbreviations: DSV= dasabuvir; DCV= daclatasvir; EASL=European Association for the Study of the Liver; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IFN=interferon; PR=pegylated interferon + ribavirin; R=ribavirin; SMV= simeprevir; SOF=sofosbuvir; LDV= ledipasvir; wk=weeks;

Table 4.4. EASL treatment recommendations for HCV-monoinfected or HCV/HIV-coinfected patients with chronic hepatitis C with compensated (Child–Pugh A) cirrhosis

Genotype	Treatment regimen							
	PR + SOF	PR + SMV	SOF + R	SOF + LDV	OBV/PTV/r + DSV	OBV/PTV/r	SOF + SMV	SOF + DCV
1a	12 wk	12 wk (treatment-naive or relapsers) or 24 wk (partial or null responders)	No	12 wk with R, or 24 wk without R, or 24 wk with R if negative predictors of response	24 wk with R	No	12 wk with R, or 24 wk without R	12 wk with R, or 24 wk without R
1b	12 wk				12 wk with R			
2	12 wk	No	16–20 wk	No	No	No	No	12 wk without R
3	12 wk	No	No	No	No	No	No	24 wk with R
4	12 wk	12 wk (treatment-naive or relapsers) or 24 wk (partial or null responders)	No	12 wk with R, or 24 wk without R, or 24 wk with R if negative predictors of response	No	24 wk with R	12 wk with R, or 24 wk without R	12 wk with R, or 24 wk without R
5 or 6	12 wk	No	No	12 wk with R, or 24 wk without R, or 24 wk with R if negative predictors of response	No	No	No	12 wk with R, or 24 wk without R

Abbreviations: DSV= dasabuvir; DCV= daclatasvir; EASL=European Association for the Study of the Liver; FDV= faldaprevir; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PR=pegylated interferon + ribavirin; R=ribavirin; SMV= simeprevir; SOF=sofosbuvir; LDV= ledipasvir; wk=weeks;

Table 4.5. EASL treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C who failed to achieve an SVR on prior antiviral therapy containing one or several DAA(s)

Failed treatment regimen	Genotype	Treatment regimen				
		SOF + LDV	OBV/PTV/r + DSV	OBV/PTV/r	SOF + SMV	SOF + DCV
PR + R + telaprevir or boceprevir	1	12 wk with R	No	No	No	12 wk with R
SOF alone, in combination with R, or in combination with PR + R	1	12 wk with R or 24 wk with R if F3 or cirrhosis	12 wk with R or 24 wk with R if F3 or cirrhosis	No	12 wk with R or 24 wk with R if F3 or cirrhosis	12 wk with R or 24 wk with R if F3 or cirrhosis
	2 or 3	No	No	No	No	
	4	12 wk with R or 24 wk with R if F3 or cirrhosis	No	12 wk with R or 24 wk with R if F3 or cirrhosis	12 wk with R or 24 wk with R if F3 or cirrhosis	
	5 or 6	12 wk with R or 24 wk with R if F3 or cirrhosis	No	No	No	
PR + R + SMV	1 or 4	12 wk with R or 24 wk with R if F3 or cirrhosis	No	No	No	
PR + R + DCV	1	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis	No
	2 or 3	No	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis
	4	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis	No
	5 or 6	12 wk with R or 24 wk with R if F3 or cirrhosis	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis
SOF + SMV	1 or 4	12 wk with R or 24 wk with R if F3 or cirrhosis	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis

SOF + DCV or SOF + LDV	1	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis	No
	2 or 3	No	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis
	4	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis	No
	5 or 6	12 wk with R or 24 wk with R if F3 or cirrhosis	No	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis
OBV/PTV/r + DSV	1	12 wk with R or 24 wk with R if F3 or cirrhosis	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis	12 wk with R or 24 wk with R if F3 or cirrhosis
OBV/PTV/r	4	12 wk with R or 24 wk with R if F3 or cirrhosis	No	No	12 wk with R or 24 wk with R if F3 or cirrhosis	12 wk with R or 24 wk with R if F3 or cirrhosis

Abbreviations: DAA=direct-acting antiviral; DSV= dasabuvir; DCV= daclatasvir; EASL=European Association for the Study of the Liver; F=stage of fibrosis; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LDV=ledipasvir; R=ribavirin; SMV= simeprevir; SOF=sofosbuvir; SVR=sustained virological response; wk=weeks.

Once defined HCV treatment, its efficacy and patient adherence to therapy should be monitored with measurements of HCV RNA levels at specific time points. According to HCV RNA level results treatment should be abandoned (the futility rule) or abbreviated (response-guided therapy). The EASL[34] identifies futility rules only with the triple combination of Peg-IFN-α, ribavirin, and simeprevir. In that case, treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24. In addition, an immediate switch to another IFN-containing DAA-containing or to an IFN-free regimen without a protease inhibitor should be considered.

Guidelines by the World Gastroenterology Organisation[136] specify futility rules for BOC-based or TVR-based triple therapy in treatment-naive patients and those in whom treatment has previously failed in case of HCV RNA level ≥100 IU/mL at 4–12 weeks or detectable result at 24 weeks.

Target population

[A0007] What is the target population of this assessment?

The target population is adult patients chronically infected with HCV genotype 1, 2, 3, 4, 5, or 6. Patients could be treatment-naive or treatment-experienced. The target population could be in any stage of HCV infection **(A0004)** (fibrosis and/or compensated/decompensated cirrhosis and/or HCC and/or other concomitant clinical condition(s)).

Each intervention has a specific target population according to approved clinical indications as reported in Table A169 in Appendix 5**.** Table A169 considered data reported in the approved summary of product characteristics.

International and national guidelines or recommendations could limit the target population or give treatment priority to specific subgroups of patients.

The EASL recommendations request that all treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy[34]. Furthermore, these guidelines recommend not to treat patients with limited life expectancy resulting from non-liver-related comorbidities **(A0025)**.

The EASL also recommends that treatment should be prioritised **(A0025)** subject to modifications according to local and/or societal considerations for specific groups of patients listed in Table 4.2.

[A0011] How much are the technologies and their comparators utilised?

The utilisation of the technology should be investigated in combination with analysis of barriers to care and treatment for patients with chronic HCV infection **(G0101)**.

Availability of public data on utilisation of anti-HCV drugs is limited.

The proportion of patients treated with antiviral drugs varies across European countries.

An analysis of 2005 data was conducted on early market uptake of Peg-IFN in 21 countries[138]. The number of patients ever treated ranged from 16% of prevalent cases in France to less than 1% of cases in Romania, Poland, Greece, and Russia.

An estimate of treatment uptake was conducted on the basis of 2002–2005 data obtained from GERS for France and IMS for other countries[73]. The number of treated patients ranged from 11% in Germany to 60% in Spain; in few cases were patients treatment-experienced. An estimate of the likelihood of being treated in the absence of alcohol abuse was conducted per fibrosis stage and on the basis of 2002–2011 data[73]. For patients with presence of alcohol abuse (> 50 g/day), the likelihood of being treated was 5 times lower than that for patients with absence of alcohol abuse.

More recent data are available for few countries.

In Belgium, according to a retrospective study on 2005–2007 data, 64% of patients with HCV were treated with either Peg-IFN-α2a or Peg-IFN-α2b, in combination with ribavirin[129]. Treatment was provided mainly to naive patients (78%), as well as those who relapsed and did not respond to previous Peg-IFN (14%).

In Germany, from 2008 to 2011, nearly all (87.3%) patients received antiviral treatment with Peg-IFN plus ribavirin[130]. Overall, 4% of them received 16-week treatment, 21.5% 24-week, 26.2% 48-week, and 8.7% received 72-week treatment. While 10.5% of patients were treated for less than 16 week and 29.1% had a different therapy duration (no further detailed).

Data on the number of treated patients, without further details on the therapy prescribed, are available for many European countries[50,60].

While uptake of telaprevir or boceprevir was low, a retrospective cross-sectional[66] study on HCV genotype 1 patients in the US in 2011–2012 showed that 18.7% of patients began triple therapy. It was the same percentage as those receiving dual therapy (Peg-IFN plus ribavirin) before boceprevir or telaprevir was approved in the US.

According to utilisation data in recent years, hepatologists employed an elective approach in order to wait to treat patients with new and improved therapies which are under assessment[139]. It is the so-called practice of **"**warehousing" patients (holding off treatment). This approach was already adopted for telaprevir and boceprevir – a rapid peak in utilisation emerged as soon as they arrived to market. A similar and stronger effect was expected and documented with sofosbuvir.

Given their recent market approval, an increase in the number of patients receiving treatment with the new DAAs is expected.

Sofosbuvir + ledipasvir and sofosbuvir reached combined sales worldwide of $4.55 billion for the first quarter of 2015. Revenue generated from sofosbuvir surpassed $10 billion in 2014.

Sales of simeprevir worldwide in the third quarter of 2014 were reported to be $796 million.

The Spanish Ministry of Health[140] announced that 18,134 HCV-infected individuals (out of a planned total of 51,900 to treat) had been treated in Spain with new drugs during the first quarter of 2015. Of these:

- 6,520 patients received ledipasvir/sofosbuvir.
- 3,849 patients received ombitasvir/paritaprevir/ritonavir plus dasabuvir..
- 6,434 patients received sofosbuvir in different combinations.
- 1,331 patients received simeprevir.

In addition to utilisation data, it's useful to analyse real-world adherence evidence. A number of factors can contribute to the difference between efficacy and effectiveness; non-adherence is one of them as well as treatment-related side effects[141].

4.3. Discussion

Chronic hepatitis C is marked by the persistence of HCV RNA in the blood for at least 6 months after the onset of acute infection (**A0002**). Increasing attention is being paid to OCI, which is characterised by the presence of HCV RNA in liver tissue or in PBMCs occurring in an individual with undetectable HCV RNA in serum, in the absence or presence of anti-HCV antibodies (**A0004**). The natural history of OCI is not yet fully defined.

The target population is adult patients chronically infected with HCV genotype 1, 2, 3, 4, 5, or 6.

To identify the eligible population, it is necessary to take into account: national incidence/prevalence of HCV; distribution of genotypes and subgroups of patients; specific target population of each intervention according to approved clinical indications; and national HCV policies.

Different sources of data to estimate HCV incidence in Europe are available. To assess the reliability of these estimates, it is necessary to pay attention to completeness and comparability of data as well as their national representativeness and definition adopted to identify HCV cases (**A0002**). Variability in prevalence as in the distribution of HCV genotypes among countries is confirmed by many epidemiological studies (**A0002**). Transferability of data is limited for estimations of HCV burden of disease, not only because of differences in demographics and epidemiology, but also in healthcare structures, and estimated costs.

The EASL recommendations request that all treatment-naive and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy. National and international guidelines identify alternative therapies for HCV patients and could define different prioritisation criteria **(A0024, A0025)**.

Heterogeneity in access to therapy between countries could be related to many causes, such as restricted reimbursement, bureaucratic obstacles, exclusion from treatment of some patients (e.g. patients with mild hepatitis), ineffective therapy policies, and screening heterogeneity.

Data on diffusion of new DAAs are currently provisional and fragmented **(A0011)**. Correct interpretation of utilisation data requires evidence of real-world adherence **(A0011)**.

5 CLINICAL EFFECTIVENESS

5.1. Research questions

Element ID	Topic / Issue	Research question
D0001	What is the expected beneficial effect of the intervention on mortality?	Indirect modelling is required for the evaluation of the effect on mortality (not planned in this project).
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition or disease?	Literature will be searched for the effect of sustained virological response (SVR) on disease progression (fibrosis, hepatocellular carcinoma [HCC]).
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?	a) How do the new treatments affect SVR at 12 weeks in relation to the comparators? b) How do the new treatments affect SVR at 24 weeks in relation to the comparators? d) How do the new treatments affect the development of resistant strains in relation to the comparators? e) How do the new treatments affect the relapse rate in relation to the comparators? f) How do the new treatments affect the long-term outcomes (decompensated liver disease, HCC, death) in relation to the comparators?
D0012 Mandatory element	What is the effect of the technology on generic health-related quality of life?	How do the new treatments affect the generic quality of life in relation to the comparators?
D0013 Mandatory element	What is the effect of the technology on disease-specific quality of life?	How do the new treatments affect the disease-specific quality of life in relation to the comparators?

5.2. Results

All studies focused in the first place on sustained virological response at 12 weeks (SVR12), which is an accepted but intermediate endpoint (see Discussion section for the use of SVR12 as a surrogate for hard clinical endpoints). In randomised controlled trials (RCTs), for interferon free combinations, patients were randomised mainly between different durations of the treatment, and between combinations with and without ribavirin (RBV). Only a very limited number of studies were found that compared regimens with different DAAs. Therefore, we considered most studies essentially as single-arm studies.

Most, but not all, studies focused on a single genotype and on treatment-naive and/or treatment-experienced patients. A limited number of studies had as inclusion criteria either patients with or without liver cirrhosis, or patients with a certain degree of fibrosis, but most considered cirrhotic state in a subgroup analysis. For studies in patients with genotype 1, genotype subtype (1a/1b) was analysed as a subgroup analysis.

We will summarise the information according to genotype and previous treatment, and present summary results according to cirrhosis status and genotype subtype. A minority of studies concerned very specific subgroups – HIV coinfected and pre- and post-transplantation patients. These studies will be treated separately. For the combinations that contain interferon (IFN), we chose to update an existing systematic review (SR) on patients with genotype 1 HCV infection.

IFN-free combinations

Genotype 1

The percentages of treatment-naive and treatment-experienced patients, with genotype 1 HCV infection, who achieved SVR12 on different IFN-free combinations, are summarised in the tables below, with 95% confidence intervals (CIs).

Information on the OPTIMIST 1 and 2 studies was provided by the MAH directly.

Treatment-naive patients

Table 5.1. SVR12 and confidence interval in genotype 1 treatment-naive patients [10,142,143]

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-1	ledipasvir + sofosbuvir	12	211	214	98.6 (96-99.7)
ION1	ledipasvir + sofosbuvir + ribavirin (NE)	12	211	217	97.2 (94.1-99)
ION-1	ledipasvir + sofosbuvir	24	212	217	97.7 (94.7-99.2)
ION-1	ledipasvir + sofosbuvir + ribavirin (NE)	24	215	217	99.1 (96.7-99.9)
LONESTAR	ledipasvir + sofosbuvir	8	19	20	95 (75.1-99.9)
LONESTAR	ledipasvir + sofosbuvir + ribavirin (NE)	8	21	21	100 (83.9-100)
LONESTAR	ledipasvir + sofosbuvir	12	18	20	90(68.3-98.8)
Mizokami	ledipasvir + sofosbuvir	12	83	83	100 (95.7-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	80	83	96.4 (89.8-99.2)
Osinusi	sofosbuvir + ribavirin patient weighted	12	17	25	68 (46.5-85.1)
Osinusi	sofosbuvir + ribavirin lower dose (NE)	12	12	25	48 (27.8-68.7)

Abbreviations: CI = confidence interval; DSV = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; PR = pegylated interferon and ribavirin; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Table 5.2. SVR12 and confidence interval in genotype 1 treatment-naive patients with cirrhosis[1,142-144]

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-1	ledipasvir + sofosbuvir	12	32	33	97 (84.2-99.9)
ION-1	ledipasvir + sofosbuvir + ribavirin (NE)	12	33	33	100 (89.4-100)
ION-1	ledipasvir + sofosbuvir	24	31	32	96.9 (83.8-99.9)
ION-1	ledipasvir + sofosbuvir + ribavirin (NE)	24	36	36	100 (90.3-100)
Mizokami	ledipasvir + sofosbuvir	12	13	13	100 (75.3-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	11	12	91.7 (61.5-99.8)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	12	81	86	94.2 (87-98.1)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	24	70	74	94.6 (86.7-98.5)
ELECTRON	ledipasvir + sofosbuvir	12	7	10	70 (34.8-93.3)
ELECTRON	ledipasvir + sofosbuvir + ribavirin (NE)	12	9	9	100 (66.4-100)

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
OPTIMIST 2	sofosbuvir + simeprevir	12	44	50	88 (75.7-95.5)

Abbreviations: CI = confidence interval; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Table 5.3. SVR12 and confidence interval in genotype 1 treatment-naive patients without cirrhosis[1,2,9,142,143,145]

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-1	ledipasvir + sofosbuvir	12	179	179	100 (98-100)
ION-1	ledipasvir + sofosbuvir + ribavirin (NE)	12	178	178	100 (97.9-100)
ION-1	ledipasvir + sofosbuvir	24	181	182	99.5 97-100)
ION-1	ledipasvir + sofosbuvir + ribavirin (NE)	24	179	179	100 (98-100)
Mizokami	ledipasvir + sofosbuvir	12	70	70	100 (94.9-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	69	71	97.2 (90.2-99.7)
ION-3	ledipasvir + sofosbuvir	8	202	215	94 (89.9-96.7)
ION-3	ledipasvir + sofosbuvir + ribavirin (NE)	8	201	216	93.1 (88.8-96.1)
ION-3	ledipasvir + sofosbuvir	12	206	216	95.4 (91.7-97.8)
SAPPHIRE-1	OBV/PTV/r + DSV + ribavirin	12	456	473	96.2 (94.1-97.7)
ELECTRON	ledipasvir + ribavirin (NE)	12	21	25	84 (63.9-95.5)
ELECTRON	Simeprevir+ paritaprevir	12	21	25	84 (63.9-95.5)
ELECTRON	ledipasvir + sofosbuvir + ribavirin (NE)	12	25	25	100 (86.3-100)
ELECTRON	ledipasvir + sofosbuvir + ribavirin (NE)	6	17	25	68 (46.5-85.1)
Sulkowski	sofosbuvir + daclatasvir	24	14	14	100 (76.8-100)
Sulkowski	sofosbuvir + daclatasvir+ ribavirin (NE)	24	15	15	100 (76.8-100)
Sulkowski	sofosbuvir + daclatasvir	12	41	41	100 (91.4-100)
Sulkowski	sofosbuvir + daclatasvir+ ribavirin (NE)	12	39	41	95.1 (83.5-99.4)
OPTIMIST- 1	sofosbuvir + simeprevir	12	112	115	97.4 (92.6-99.5)
OPTIMIST- 1	sofosbuvir + simeprevir (NE)	8	88	103	85.4 (77.1-91.6)

Abbreviations: CI = confidence interval; DSV = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; PR = pegylated interferon and ribavirin; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Treatment-experienced patients

Table 5.4. SVR12 and confidence interval in genotype 1 treatment-experienced patients[10,143,146,147]

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-2	ledipasvir + sofosbuvir	12	102	109	93.6 (87.2-97.4)
ION-2	ledipasvir + sofosbuvir + ribavirin (NE)	12	107	111	96.4 (91-99)
ION-2	ledipasvir + sofosbuvir	24	108	109	99.1 (95-100)
ION-2	ledipasvir + sofosbuvir + ribavirin (NE)	24	110	111	99.1 (95.1-100)
LONESTAR	ledipasvir + sofosbuvir	12	18	19	94.7 (74 -99.9)
LONESTAR	ledipasvir + sofosbuvir + ribavirin (NE)	12	21	21	100 (83.9-100)
Osinusi	ledipasvir + sofosbuvir	12	14	14	100 (76.8-100)
Mizokami	ledipasvir + sofosbuvir	12	88	88	100 (95.9-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	87	87	100 (95.8-100)

Abbreviations: CI = confidence interval; LDV = ledipasvir; LL = lower limit; R = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Table 5.5. SVR12 and confidence interval in genotype 1 treatment-experienced patients with cirrhosis[143,144,146,148]

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-2	ledipasvir + sofosbuvir	12	19	22	86.4 (65.1-97.1)
ION-2	ledipasvir + sofosbuvir + ribavirin (NE)	12	18	22	81.8 (59.7-94.8)
ION-2	ledipasvir + sofosbuvir	24	22	22	100 (84.6-100)
ION-2	ledipasvir + sofosbuvir + ribavirin (NE)	24	22	22	100 (84.6-100)
Mizokami	ledipasvir + sofosbuvir	12	28	28	100 (87.7-100)
Mizokami	ledipasvir + sofosbuvir + ribavirin (NE)	12	23	23	100 (85.2-100)
SIRIUS	ledipasvir + sofosbuvir + ribavirin (NE)	12	74	77	97.4 (90.9-99.7)
SIRIUS	ledipasvir + sofosbuvir	12	75	77	97.4 (90.9-99.7)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	12	110	122	90.2 (83.4-94.8)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	24	95	98	96.9 (91.3-99.4)
OPTIMIST-2	sofosbuvir + simeprevir	12	42	53	79.2 (65.9-89.2)

Abbreviations: CI = confidence interval; DSV = dasabuvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Table 5.6. SVR12 and confidence interval in genotype 1 treatment-experienced patients without cirrhosis[1,2,143,146,149-151]

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION - 2	ledipasvir + sofosbuvir	12	83	87	95.4 (88.6-98.7)
ION - 2	ledipasvir + sofosbuvir + ribavirin (NE)	12	89	89	100 (95.9-100)
ION - 2	ledipasvir + sofosbuvir	24	86	87	98.9 (93.8-100)
ION - 2	ledipasvir + sofosbuvir + ribavirin (NE)	24	88	89	98.9 (93.8-100)
Mizokami	ledipasvir + sofosbuvir	12	60	60	100 (94-100)
Mizokami	ledipasvir + sofosbuvir	12	64	64	100 (94-100)

Study	Treatment combination	Duration of treatment (weeks)	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
	+ ribavirin (NE)				
SAPPHIRE-II	OBV/PTV/r + DSV + ribavirin	12	286	297	96.3 (93.5-98.1)
COSMOS	simeprevir + sofosbuvir + ribavirin	24	19	24	79.2 (57.8-92.9)
COSMOS	simeprevir + sofosbuvir	24	14	15	93.3 (68.1-99.8)
COSMOS	simeprevir + sofosbuvir + ribavirin	12	26	27	96.3 (81-99.9)
COSMOS	simeprevir + sofosbuvir	12	13	14	92.9 (66.1-99.8)
ELECTRON	sofosbuvir + ribavirin	12	1	10	10 (0.3-44.5)
Sulkowski	sofosbuvir + daclatasvir	24	21	21	100 (83.9-100)
Sulkowski	sofosbuvir + daclatasvir + ribavirin (NE)	24	19	20	95 (75.1-99.9)
OPTIMIST-1	simeprevir + sofosbuvir	12	38	40	95 (83.1-99.4)
OPTIMIST-1	simeprevir + sofosbuvir (NE)	8	40	52	76.3 (63.2-87.5)

Abbreviations: CI = confidence interval; DSV = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

The treatments that combine at least 2 of the new DAAs show SVR rates above 95% in nearly all study arms. These SVR rates remain high across subgroups. In treatment-experienced patients with cirrhosis, the data show a tendency towards somewhat lower SVR rates than those seen in treatment-naive or non-cirrhotic patients, but sample sizes are too small to demonstrate this difference in a statistically significant way, as most studies were only powered to detect differences of 15%.

For the combination simeprevir (SMV) + sofosbuvir (SOF), only the COSMOS study was published as full text. The results of the OPTIMIST-1 and OPTIMIST-2 studies only appeared in abstract form. However, in their submission document, the company provided further details. Therefore, we decided to include them, although we did not have the full text.

Studies that randomised study arms with and without RBV showed no statistically significant difference between the treatment arms for SVR12, although in most studies SVR was somewhat higher in the RBV arm, typically around 5%. However, as mentioned earlier, studies were powered to detect differences of 15% at most. In order to demonstrate a difference of 5% from a baseline of 95%, with a power of 80% and an alpha error of 5%, 431 subjects in each arm would be needed. The same is true for randomisations between treatment durations of 8, 12, and 24 weeks.

We present most data for treatment-naive and treatment-experienced patients separately, because most studies had either treatment-naive or treatment-experienced patients as an entry criterion. Some studies provided results per treatment response; we extracted those data but did not summarise them here, results depending because the numbers were too small to provide meaningful results. SVR rates are similar in treatment-experienced and treatment-naive patients, with a tendency towards a somewhat lower SVR rate in cirrhotic, treatment-experienced patients, although the numbers are too small to provide conclusive statements on such a limited difference.

The data concerning cirrhosis come from a mix of studies that had either cirrhotic or non-cirrhotic as an entry criterion, and a subgroup analysis of mixed studies. SVR12 rates are similar in cirrhotic and non-cirrhotic patients, with a tendency towards a somewhat lower SVR12 rate in cirrhotic, treatment-experienced patients, although the numbers are too small to provide conclusive statements on such a limited difference.

Subgroups genotype 1a/1b

Table 5.7. SVR12 and confidence interval in genotype 1a/1b treatment-naive patients[144,146,149,150,152,153]

Study	Treatment combination	Duration of treatment	Subtype	Fibrosis	Subjects with SVR12	Subjects studied	SVR12 (95% CI) (%)

		(weeks)			(N)	(N)	
ION -1	ledipasvir + sofosbuvir	12	1a	Mix	141	142	99.3 (96.1-100)
ION -1	ledipasvir + sofosbuvir + ribavirin (NE)	12	1a	Mix	143	143	100 (97.5-100)
ION -1	ledipasvir + sofosbuvir	24	1a	Mix	143	143	100 (97.5-100)
ION -1	ledipasvir + sofosbuvir + ribavirin (NE)	24	1a	Mix	141	141	100 (97.4-100)
ION -1	ledipasvir + sofosbuvir	12	1b	Mix	66	66	100 (94.6-100)
ION -1	ledipasvir + sofosbuvir + ribavirin (NE)	12	1b	Mix	67	67	100 (94.9-100)
ION -1	ledipasvir + sofosbuvir	24	1b	Mix	66	66	97.1 (89.8-99.6)
ION -1	ledipasvir + sofosbuvir + ribavirin (NE)	24	1b	Mix	71	71	100 (94.9-100)
ION -3	ledipasvir + sofosbuvir	12	1a	No cirrhosis	163	172	94.8 (90.3-97.6)
ION -3	ledipasvir + sofosbuvir	12	1b	No cirrhosis	43	44	97.7 (88-99.9)
SAPPHIRE-I	OBV/PTV/r + DSV + ribavirin	12	1a	No cirrhosis	308	322	95.3 (92.4-97.4)
SAPPHIRE-I	OBV/PTV/r + DSV + ribavirin	12	1b	No cirrhosis	148	151	98 (94.3-99.6)
PEARL-IV	OBV/PTV/r + DSV + ribavirin	12	1a	No cirrhosis	97	100	97 (91.5-99.4)
PEARL-IV	OBV/PTV/r + DSV (NE)	12	1a	No cirrhosis	185	205	90.2 (85.3-93.9)
PEARL-III	OBV/PTV/r + DSV + ribavirin (NE)	12	1b	No cirrhosis	209	210	99.5 (97.4-100)
PEARL-III	OBV/PTV/r + DSV	12	1b	No cirrhosis	209	209	100 (98.3-99.9)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	12	1a	Cirrhosis	59	64	92.2 (82.7-97.4)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	24	1a	Cirrhosis	53	56	946 (85.1-98.9)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	12	1b	Cirrhosis	22	22	100 (84.6-100)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	24	1b	Cirrhosis	18	18	100 (81.5-100)
Pearlman	simeprevir + sofosbuvir	12	1a	Mix	21	22	95.5 (77.2-99.9)

Abbreviations: CI = confidence interval; DSV = dasabuvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Table 5.8. SVR12 and confidence interval in genotype 1a/1b treatment-experienced patients[10,144,148,149,151,153]

Study	Treatment combination	Duration of treatment (weeks)	Genotype / subtype	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION -2	ledipasvir + sofosbuvir	12	1a	Mix	82	86	95.3 (88.5-98.7)
ION -2	ledipasvir + sofosbuvir + ribavirin (NE)	12	1a	Mix	84	88	95.5 (88.8-98.7)
ION -2	ledipasvir + sofosbuvir	24	1a	Mix	84	85	98.8 (93.6-100)
ION -2	ledipasvir + sofosbuvir + ribavirin (NE)	24	1a	Mix	87	88	98.9 (93.8-100)
ION -2	ledipasvir + sofosbuvir	12	1b	Mix	20	23	87 (66.4-97.2)
ION -2	ledipasvir + sofosbuvir + ribavirin (NE)	12	1b	Mix	23	23	100 (85.2-100)
ION -2	ledipasvir + sofosbuvir	24	1b	Mix	24	24	100 (85.8-100)
ION -2	ledipasvir + sofosbuvir + ribavirin (NE)	24	1b	Mix	23	23	100 (85.2-100)
SIRIUS	ledipasvir + sofosbuvir + ribavirin (NE)	12	1a	Cirrhosis	47	48	97.9 (88.9-99.9)
SIRIUS	ledipasvir + sofosbuvir	24	1a	Cirrhosis	48	49	98 (89.1-99.9)
SIRIUS	ledipasvir + sofosbuvir + ribavirin (NE)	12	1b	Cirrhosis	26	28	92.9 (76.5-99.1)
SIRIUS	ledipasvir + sofosbuvir	24	1b	Cirrhosis	26	27	96.3 (81-99.9)
SAPPHIRE-I	OBV/PTV/r + DSV + ribavirin	12	1a	No cirrhosis	166	173	96.0 (91.8-98.4)
SAPPHIRE-I	OBV/PTV/r + DSV + ribavirin (NE)	12	1b	No cirrhosis	119	123	96.7 (91.9-99.1)
PEARL-II	OBV/PTV/r + DSV + ribavirin (NE)	12	1b	No cirrhosis	86	88	97.7(92.0-99.7)
PEARL-II	OBV/PTV/r + DSV	12	1b	No cirrhosis	91	91	100 (96-100)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	12	1a	Cirrhosis	65	76	85.5 (75.6-92.5)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	24	1a	Cirrhosis	62	65	95.4 (87.1-99.0)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin	12	1b	Cirrhosis	45	46	97.8 (88.5-99.9)
TURQUOISE-II	OBV/PTV/r + DSV + ribavirin (NE)	24	1b	Cirrhosis	33	33	100 (89.4-100)
Pearlman	simeprevir + sofosbuvir	12	1a	Mix	33	36	91.7 (77.5-98.2)

Abbreviations: CI = confidence interval; DSV = dasabuvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

SVR12 rates are similar in genotype 1a and 1b patients, with a tendency towards a somewhat lower SVR12 rate in 1b patients, although the numbers are too small to provide conclusive statements on such a limited difference. The same is true for viral load, with somewhat lower SVR rates for patients with higher viral loads at baseline. We did not summarise these data, but they can be found in the extraction tables.

Genotypes 2 - 4

We present the data on patients with genotypes 2 and 3 in the Tables below, together with the subgroup analyses that were possible given the data. A number of studies grouped patients with genotypes 2 and 3 and reported the data in such a way that it was not possible to separate them. These results are reported in a separate table.

Table 5.9. SVR12 and confidence interval in genotype 2 patients[145,150,154-158]

Study	Treatment combination	Duration of treatment (weeks)	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
POSITRON	sofosbuvir + ribavirin	12	Mix	101	109	92.7 (86-96.8)
FUSION	sofosbuvir + ribavirin	12	Mix	31	36	86.1 (70.5-95.3)
FUSION	sofosbuvir + ribavirin	16	Mix	30	32	93.8 (79.2-99.2)
Omata	sofosbuvir + ribavirin	12	Mix	148	153	96.7 (92.5-98.9)
Omata	sofosbuvir + ribavirin	12	Mix	88	90	97.8 (92.2-99.7)
Omata	sofosbuvir + ribavirin	12	Mix	60	63	95.2 (86.7-99.0)
Omata	sofosbuvir + ribavirin	12	Cirrhosis	16	17	94.1 (71.3-99.9)
VALENCE	sofosbuvir + ribavirin	12	Mix	68	73	93.2 (84.7-97.7)
BOSON	sofosbuvir + ribavirin	16	Mix	13	15	86.7 (59.5-98.3)
BOSON	sofosbuvir + ribavirin	24	Mix	17	17	100 (80.5-100)
FISSION	sofosbuvir + ribavirin	12	Mix	68	70	97.1 (90.1-99.7)

Abbreviations: CI = confidence interval; LL = lower limit; R = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit

Table 5.10. SVR12 and confidence interval in genotype 3 patients[1,2,145,155,156,158,159]

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
POSITRON	sofosbuvir + ribavirin (NE)	12	Mostly naive	Mix	60	98	61.2 (50.8-70.9)
FUSION	sofosbuvir + ribavirin (NE)	12	Experienced	Mix	19	64	29.7 (18.9-42.4)
FUSION	sofosbuvir + ribavirin (NE)	16	Experienced	Mix	39	63	61.9 (48.8-73.9)
VALENCE	sofosbuvir +	12	Mix	Mix	3	11	27.3 (6-61)

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
	ribavirin (NE)						
VALENCE	sofosbuvir + ribavirin	24	Mix	Mix	213	250	85.2 (80.2-89.4)
VALENCE	sofosbuvir + ribavirin	24	Naive	No cirrhosis	87	92	94.6 (87.8-98.2)
VALENCE	sofosbuvir + ribavirin	24	Naive	Cirrhosis	12	13	92.3 (64-99.8)
VALENCE	sofosbuvir + ribavirin	24	Experienced	No cirrhosis	85	98	86.7 (78.4-92.7)
VALENCE	sofosbuvir + ribavirin	24	Experienced	Cirrhosis	29	47	61.7 (46.4-75.5)
VALENCE	sofosbuvir + ribavirin	24	Mix	No cirrhosis	173	190	91.1 (86.1-94.7)
VALENCE	sofosbuvir + ribavirin	24	Mix	Cirrhosis	41	60	68.3 (55-79.7)
BOSON	sofosbuvir + ribavirin (NE)	16	Mix	Mix	128	181	70.7 (63.5-77.2)
BOSON	sofosbuvir + ribavirin	24	Mix	Mix	153	182	84.1 (77.9-89.1)
BOSON	sofosbuvir + ribavirin (NE)	16	Naive	Mix	70	91	76.9 (66.9-85.1)
BOSON	sofosbuvir + ribavirin	24	Naive	Mix	83	94	88.3 (80-94)
BOSON	sofosbuvir + ribavirin (NE)	16	Naive	No cirrhosis	58	70	82.9 (72-90.8)
BOSON	sofosbuvir + ribavirin	24	Naive	No cirrhosis	65	72	90.3 (81-96)
BOSON	sofosbuvir + ribavirin (NE)	16	Naive	Cirrhosis	12	21	57.1 (34-78.2)
BOSON	sofosbuvir + ribavirin	24	Naive	Cirrhosis	18	22	81.8 (59.7-94.8)
BOSON	sofosbuvir + ribavirin (NE)	16	Experienced	Mix	58	90	64.4 (53.7-74.3)
BOSON	sofosbuvir + ribavirin	24	Experienced	Mix	70	88	79.5 (69.6-87.4)
BOSON	sofosbuvir + ribavirin (NE)	16	Experienced	No cirrhosis	41	54	75.9 (62.4-86.5)
BOSON	sofosbuvir + ribavirin	24	Experienced	No cirrhosis	44	54	81.5 (68.6-90.7)
BOSON	sofosbuvir + ribavirin (NE)	16	Experienced	Cirrhosis	17	36	47.2 (30.4-64.5)
BOSON	sofosbuvir + ribavirin	24	Experienced	Cirrhosis	26	34	76.5 (58.8-89.3)
FISSION	sofosbuvir + ribavirin (NE)	12	Naive	Mix	102	183	55.7 (48.2-63.1)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Naive	Mix	91	101	90.1 (82.5-95.1)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Experienced	Mix	44	51	86.3 (73.7-94.3)
ALLY-3	sofosbuvir + daclatasvir	12	Naive	No cirrhosis	73	75	97.3 (90.7-99.7)

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
	(NE)						
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Naive	Cirrhosis	11	19	57.9 (33.5-79.7)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Experienced	No cirrhosis	32	34	94.1 (80.3-99.3)
ALLY-3	sofosbuvir + daclatasvir (NE)	12	Experienced	Cirrhosis	9	13	69.2 (38.6-90.9)

CI = confidence interval; DCV = daclatasvir; LL = lower limit; R = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Generally, SVR12 rates for the combination of SOF+RBV were reported for genotype 2 patients, and studies consistently show SVR12 rates around 95%, except in the FUSION study. However, CIs in some studies are wide and, in some arms, the 95% CI did not include 90%.

The combination SOF+RBV seems to have a lower SVR12 rate in genotype 3 patients compared to genotype 2 patients, although numbers are small and CIs wide. Daclatasvir (DCV) + SOF shows higher SVR12 rates in non-cirrhotic patients but a tendency towards lower SVR12 rates in cirrhotic patients, although numbers are low and 95% CI are wide.

In 2 studies results were not reported separately for genotype 2 and 3. Numbers are small though.

Table 5.11. SVR12 and confidence interval in genotypes 2 and 3 patients, in studies where the groups were not reported separately[1,2]

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ELECTRON	sofosbuvir + ribavirin	12	Naive	No cirrhosis	10	10	100 (69.2-100)
Sulkowski	sofosbuvir + daclatasvir	24	Naive	No cirrhosis	14	14	100 (76.8-100)
Sulkowski	sofosbuvir + daclatasvir + ribavirin	24	Naive	No cirrhosis	12	14	85.7 (57.2. -98.2)

Abbreviations: CI = confidence interval; LL = lower limit; R = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit

Table 5.12. SVR12 and confidence interval in genotype 4 patients[150,160,161]

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
PEARL-I	OBV/PTV/r + DSV (NE)	12	Naive	No cirrhosis	40	44	90.9 (78.3-97.5)
PEARL-I	OBV/PTV/r + DSV + ribavirin	12	Naive	No cirrhosis	42	42	100 (91.6-100)
PEARL-I	OBV/PTV/r +	12	Experienced	No	49	49	100 (92.7-100)

Study	Treatment combination	Duration of treatment (weeks)	Naive status	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
	DSV + ribavirin			cirrhosis			
Ruane	sofosbuvir + ribavirin	12	Mix	Mix	21	31	67.7 (48.6-83.3)
Ruane	sofosbuvir + ribavirin	12	Naive	Mix	11	14	78.6 (49.2-95.3)
Ruane	sofosbuvir + ribavirin	12	Experienced	Mix	10	17	58.8 (32.9-81.6)
Ruane	sofosbuvir + ribavirin	24	Mix	Mix	27	29	93.1 (77.2-99.2)
Ruane	sofosbuvir + ribavirin	24	Naive	Mix	14	14	100 (76.8-100)
Ruane	sofosbuvir + ribavirin	24	Experienced	Mix	13	15	86.7 (59.5-98.3)
Kohli	ledipasvir + sofosbuvir	12	Mix	Mix	20	21	95.2 (76.2-99.9)

Abbreviations: CI = confidence interval; DSV = dasabuvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; R = ribavirin; RIT = ritonavir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

In genotype 4 patients, the combination ombitasvir (OBV) + paritaprevir (PTV) + ritonavir (RIT), without dasabuvir (DSV) (OBV/PTV/r12 excluding DSV), + RBV shows a SVR12 rate of 100%, with the 95% CI not including 90%. Evidence for SOF+RBV is mixed, showing a tendency towards lower SVR12 rates, with lower limits of the 95% CI under 50%. Only one small study was found for ledipasvir (LDV) + SOF, showing a SVR12 rate of 95%, with the lower 95% CI not including 75%.

IFN-containing combinations

Genotype 1

We updated the Canadian SR[13] for genotype 1 patients; a full summary can be found in Appendix 1. We summarise the main findings here, together with the update. The Canadian SR meta-analysed the studies both in a network meta-analysis (NMA) and in direct comparison, where direct comparisons were available, which we consider as valid. Details on the methods used in the analysis are put in appendix. In short, data that were homogenous in terms of study and patient characteristics were pooled using standard meta-analysis methods with Review Manager 5.2 software.52 Random effects models were used if I2 values exceeded 50% or if statistical heterogeneity was present. We put details on the method in appendix. However, we only report the meta-analysed results of the direct comparisons, because all indirect comparisons were inconclusive due to lack of power, none was statistically significant and confidence intervals were too wide to be informative. Therefore, we decided there would be no added value from reporting these. For the other genotypes, we summarised the results of our search.

SMV+PR

In total, 5 individual studies were included in the review, 3 for treatment-naive patients with a total of 1,171 patients (PILLAR, QUEST-1, and QUEST-2) and 2 for treatment-experienced patients (ASPIRE and PROMISE) with a total of 855 patients. Treatment-experienced patients were either relapsers (ASPIRE and PROMISE), or partial or null responders (ASPIRE) to previous pegylated interferon and ribavirin (PR) therapy; the criteria used to define relapse were similar across the 2 studies. All 5 studies compared SMV+PR with 48 weeks of PR therapy plus placebo, and all were included in the NMA.

SVR12 results in treatment-naive patients

Among treatment-naive patients with genotype 1 HCV infection treated with SMV+PR for 24 or 48 weeks, the SVR12 rate across 3 studies ranged from 80% to 81%, whereas it was only 50% to

66% for patients treated with PR alone for 48 weeks. Additionally, the SVR12 rate in patients with genotype 1b was higher (82%-90%; 2 studies) than in patients with genotype 1a (71%-80%; 2 studies). In patients with cirrhosis, the SVR12 rate ranged from 66% to 70% in 2 studies, whereas in patients without cirrhosis it ranged from 83% to 85% in 2 studies. The SVR12 rates in patients treated with PR alone for 48 weeks were lower than in patients treated with SMV+PR for 24 or 48 weeks, across all subgroups, and ranged from 28% to 67%.

Table 5.13. Genotype 1 – Treatment-naive patients – overall[13]

Study	Treatment combination	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
QUEST-1	PR 2a for 48 weeks	65	130	50 (41.1-58.9)
QUEST-1	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	210	264	79.5 (74.2-84.2)
QUEST-2	PR for 48 weeks	67	134	50 (41.2-58.8)
QUEST-2	Simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	209	257	81.3 (76-85.9)
PILLAR	PR 2a for 48 weeks	51	77	66.2 (54.6-76.6)
PILLAR	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	62	77	80.5 (69.9-88.7)

Abbreviations: 2a = peginterferon alfa 2a; 2b = peginterferon alfa 2b; CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SMV = simeprevir; SVR = sustained virological response; UL = upper limit

Table 5.14. Genotype 1 – Treatment-naive patients – Genotype subtype 1a[13]

Study	Treatment combination	Genotype / subtype	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
QUEST-1	PR 2a for 48 weeks		36	74	48.6 (36.9-60.6)
QUEST-1	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT		105	147	71.4 (63.4-78.6)
QUEST-1	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	With Q80K	31	60	51.7 (38.4-64.8)
QUEST-1	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	Without Q80K	73	86	84.9 (75.5-91.7)
QUEST-2	PR for 48 weeks		26	57	45.6 (32.4-59.3)
QUEST-2	Simeprevir for 12 weeks + PR for 24 or 48 weeks RGT		86	107	80.4 (71.6-87.4)
QUEST-2	Simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	With Q80K	18	24	75 (53.3-90.2)
QUEST-2	Simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Without Q80K	65	79	82.3 (72.1-90)

Abbreviations: 2a = peginterferon alfa 2a; 2b = peginterferon alfa 2b; CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SMV = simeprevir; SVR = sustained virological response; UL = upper limit

Table 5.15. Genotype 1 – Treatment-naive patients – Genotype subtype 1b[13]

Study	Treatment combination	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)

Study	Treatment combination	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
QUEST-1	PR 2a for 48 weeks	29	56	51.8 (38-65.3)
QUEST-1	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	105	117	89.7 (82.8-94.6)
QUEST-2	PR for 48 weeks	41	77	53.2 (41.5-64.7)
QUEST-2	Simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	123	150	82.0 (74.9-87.8)

Abbreviations: 2a = peginterferon alfa 2a; 2b = peginterferon alfa 2b; CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SMV = simeprevir; SVR = sustained virological response; UL = upper limit

Table 5.16. Genotype 1 – Treatment-naive patients – Cirrhosis subgroup[13]

Study	Treatment combination	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
QUEST-1	PR 2a for 48 weeks	F3-F4	11	40	27.5 (14.6-43.9)
QUEST-1	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	F3-F4	54	77	70.1 (58.6-80)
QUEST-2	PR for 48 weeks	F3-F4	15	32	46.9 (29.1-65.3)
QUEST-2	Simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	F3-F4	35	53	66 (51.7-78.5)

Abbreviations: 2a = peginterferon alfa 2a; 2b = peginterferon alfa 2b; CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SMV = simeprevir; SVR = sustained virological response; UL = upper limit

Table 5.17. Genotype 1 – Treatment-naive patients – No cirrhosis subgroup[13]

Study	Treatment combination	Fibrosis	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
QUEST-1	PR 2a for 48 weeks	F0-F2	54	90	60 (49.1-70.2)
QUEST-1	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	F0-F2	152	183	83.1 (76.8-88.2)
QUEST-2	PR for 48 weeks	F0-F2	52	102	51 (40.9-61)
QUEST-2	Simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	F0-F2	165	195	84.6 (78.8-89.4)
PILLAR	PR 2a for 48 weeks	No cirrhosis	19	29	65.5 (45.7-82.1)
PILLAR	PR 2a for 48 weeks	No cirrhosis	31	48	64.6 (49.5-77.8)
PILLAR	PR 2a for 48 weeks	No cirrhosis	51	77	66.2 (54.6-76.6)
PILLAR	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	No cirrhosis	62	77	80.5 (69.9-88.7)

Abbreviations: 2a = peginterferon alfa 2a; 2b = peginterferon alfa 2b; CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SMV = simeprevir; SVR = sustained virological response; UL = upper limit

A direct pairwise comparison of the SVR12 rate between the two regimens across 3 studies including 939 patients showed a risk difference of 27% (95% CI 18 to 35) and a relative risk of 1.48 (95% CI 1.25 to 1.75) in favour of SMV+PR. In terms of fibrosis severity and genotype subtype, all relative risks were in favour of SMV+PR although, in patients with genotype subtype 1a with Q80K, this was not statistically significant.

Table 5.18. Treatment-naive patients – Direct pairwise comparison of SVR overall, by fibrosis severity, and by genotype subtype[13]

DAA vs. PR48	Population	N Trials	N Patients	SVR	
				RD% (95%CI), I² %	RR (95%CI), I² %
simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Overall	3	939	27 (18-35), I^2=45%	1.48 (1.25-1.75), I^2=59%
	F0-F2	2	570	28 (18-39), I^2=41%	1.51 (1.26-1.80), I^2=43%
	F3-F4		202	32 (9-55), I^2=64%	1.86 (1.02-3.38), I^2=69%
	1a	2	385	28 (17-40), I^2=26%	1.59 (1.31-1.93), I^2=0%
	1a with Q80K		215	15 (-11-41), I^2=72%	1.31 (0.85-2.03), I^2=67%
	1a without Q80K		296	36 (26-47), I^2=0%	1.77 (1.46-2.14), I^2=0%
	1b		400	33 (23-42), I^2=0%	1.62 (1.37-1.92), I^2=0%

Abbreviations: CI = confidence interval; PR = pegylated interferon and ribavirin; RD = risk difference; RGT = response-guided therapy; RR = relative risk; SMV = simeprevir; SVR = sustained virological response I2 Higgins I2, measure of heterogeneit

Note: In the update, we found a number of studies that investigated a lower dose of SMV than the dose recommended in the SmPC in the EPAR[7,8,11,12] (CONCERTO 1-4, DRAGON). We do not report these results.

SVR12/SVR24 results in treatment-experienced patients

Among treatment-experienced patients with genotype 1 HCV infection treated with SMV+PR for 24 or 48 weeks, the SVR12/SVR24 rate across 2 studies ranged from 67% to 79%, whereas it was only between 23% and 37% for patients treated with PR alone for 48 weeks. In terms of previous treatment experience, the SVR12/SVR24 rate was highest for relapsers (77%-79%; 2 studies), followed by partial responders (65%) and null responders (53%). Concerning genotype, the SVR12 rate was higher in patients with genotype 1b than in patients with genotype 1a (86% vs 70%, respectively). Patients without cirrhosis showed a higher SVR12 rate than patients with cirrhosis (82% vs 73%, respectively). In comparison, the SVR12/SVR24 rates in patients treated with PR alone for 48 weeks were lower than in patients treated with SMV+PR for 24 or 48 weeks, across all subgroups, and ranged from 9% to 43%.

Table 5.19. Genotype 1 – Treatment-experienced patients – overall[13]

Study	Treatment combination	Other	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ASPIRE	PR 2a for 48 weeks	SVR24	15	66	22.7 (13.3-34.7)
ASPIRE	Simeprevir for 12 weeks + PR 2a for 48 weeks	SVR24	44	66	66.7 (54-77.8)
PROMISE	PR 2a for 48 weeks	Relapser	49	133	36.8 (28.6-45.6)
PROMISE	Simeprevir for 12 weeks + PR 2a for 24 or 48 weeks RGT	Relapser	206	260	79.2 (73.8-84)

Abbreviations: 2a = peginterferon alfa 2a; CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SMV = simeprevir; SVR = sustained virological response; UL = upper limit

A direct pairwise comparison of the SVR24 rate between SMV12+PR for 48 weeks and PR alone for 48 weeks, including one study of 393 patients, showed a risk difference of 44% (95% CI 29 to 59) and a relative risk of 2.93 (95% CI 1.82 to 4.72) in favour or SMV+PR; both were statistically significant (P<0.001). A direct pairwise comparison of the SVR12 rate of SMV12+PR for 24 or 48 weeks compared with PR alone for 48 weeks, including one study of 132 patients, yielded a risk difference of 42% (95% CI 33 to 52) and a relative risk of 2.15 (95% CI 1.71 to 2.71) in favour of SMV+PR; both

were statistically significant (P < 0.001). Concerning fibrosis severity and genotype subtype, all relative risks were in favour of SMV+PR although, in patients with genotype subtype 1a with Q80K, this was not statistically significant.

Table 5.20. Treatment-experienced patients – Direct pairwise comparison of SVR overall, by fibrosis severity, and by genotype subtype[13]

DAA vs. PR48	Population	N Trials	N Patients	SVR	
				RD% (95%CI), P-value	RR (95%CI), P-value
simeprevir for 12 weeks + PR for 48 weeks	Overall	1	132	44 (29-59), P<0.001	2.93 (1.82-4.72), P<0.001
simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Overall	1	393	42 (33-52), P<0.001	2.15 (1.71-2.71), P<0.001
	F0-F2	1	265	41 (30-53)	2.01 (1.57-2.58)
	F3-F4		117	50 (33-67)	3.12 (1.68-5.8)
	1a	1	165	42 (28-57)	2.53 (1.62-3.95)
	1a with Q80K		84	19 (-3-40)	1.68 (0.94-2.99)
	1a without Q80K		133	51 (36-66)	2.83 (1.81-4.41)
	1b		228	43 (31-55)	2 (1.54-2.59)

Abbreviations: CI = confidence interval; PR = pegylated interferon and ribavirin; RD = risk difference; RGT = response-guided therapy; RR = relative risk; SMV = simeprevir; SVR = sustained virological response

In the update, we found one study comparing SMV+PR with telaprevir+PR, with subgroup analysis of genotype subtype and cirrhotic state[162].

Table 5.21. SVR12 of TEL12+PR48 compared to SMV12+PR48, overall, according to subgenotype1a/1b and in patients with cirrhosis

Study	Treatment combination	Genotype/ subtype	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ATTAIN	telaprevir for 12 weeks + PR for 48 weeks	1	Mix	210	384	54.7 (49.6-59.7)
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1	Mix	203	379	53.6 (48.4-58.7)
ATTAIN	telaprevir for 12 weeks + PR for 48 weeks	1a	Mix	63	164	38.4 (30.9-46.3)
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1a	Mix	66	164	40.2 (32.7-48.2)
ATTAIN	telaprevir for 12 weeks + PR for 48 weeks	1b	Mix	147	220	66.8 (60.2-73)
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1b	Mix	137	215	63.7 (56.9-70.2)
ATTAIN	telaprevir for 12 weeks + PR for 48 weeks	1	Cirrhosis	19	51	37.3 (24.1-51.9)
ATTAIN	simeprevir for 12 weeks + PR for 48 weeks	1	Cirrhosis	20	57	35.1 (22.9-48.9)

Abbreviations: CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; SMV = simeprevir; SVR = sustained virological response; TEL = telaprevir; UL = upper limit

Overall difference was -1·1%, 95% CI -7·8 to 5·5; P=0·0007 (p value for a non-inferiority margin of 12%).

SOF+PR

SVR12 results in treatment-naive patients

Among treatment-naive patients with genotype 1 HCV infection treated with SOF+PR, the SVR12 rate across 3 studies ranged from 89% to 91%, independently of the duration of PR therapy (12 weeks vs 24/48 weeks response-guided therapy [RGT]). In comparison, among patients treated with PR alone for 48 weeks, the SVR12 rate was 58% (1 study). In addition, the SVR12 rate was higher both in patients with genotype 1a than in patients with genotype 1b (92% vs 82%, respectively) and in patients without cirrhosis than in patients with cirrhosis (92% vs 80%, respectively).

Table 5.22. Genotype 1 – Treatment-naive patients – overall and in subgroups[13]

Study	Treatment combination	Genotype/ subtype	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ATOMIC	sofosbuvir for 12 weeks + PR 2a for 12 weeks	1	No cirrhosis	47	52	90.4 (79-96.8)
NEUTRINO	sofosbuvir for 12 weeks + PR 2a for 12 weeks	incl. 35 patients with genotype 4,5,6	?	261	292	89.4 (85.3-92.7)
NEUTRINO	sofosbuvir for 12 weeks + PR 2a for 12 weeks	1a	?	206	225	91.6 (87.1-94.8)
NEUTRINO	sofosbuvir for 12 weeks + PR 2a for 12 weeks	1b	?	54	66	81.8 (70.4-90.2)
NEUTRINO	sofosbuvir for 12 weeks + PR 2a for 12 weeks	1	F4	43	54	79.6 (66.5-89.4)
NEUTRINO	sofosbuvir for 12 weeks + PR 2a for 12 weeks	1	F3-F4	252	273	92.3 (88.5-95.2)
PROTON	PR 2a for 48 weeks	1	No cirrhosis	15	26	57.7 (36.9-76.6)
PROTON	sofosbuvir for 12 weeks + PR 2a for 12 or 24 weeks RGT	1	No cirrhosis	43	47	91.5 (79.6-97.6)

Abbreviations: 2a = peginterferon alfa 2a; CI = confidence interval; LL = lower limit; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit

A direct pairwise comparison of the SVR12 rate between SOF12+PR for 24 or 48 weeks, including one study of 73 patients, yielded a risk difference of 32% (95% CI 11 to 53) and a relative risk of 1.55 (95% CI 1.10 to 2.18) in favour or SOF+PR for 48 weeks.

Table 5.23. Treatment-naive patients – Direct pairwise comparison of SVR[13]

DAA vs. PR48	N Trials	N Patients	SVR	
			RD% (95%CI)	RR (95%CI)
sofosbuvir for 12 weeks + PR for 24 or 48 weeks RGT	1	73	32 (11-53),	1.55 (1.10-2.18),

Abbreviations: CI = confidence interval; PR = pegylated interferon and ribavirin; RD = risk difference; RGT = response-guided therapy; RR = relative risk; SMV = simeprevir; SVR = sustained virological response

IFN-containing regimens genotypes 2, 3, and 4[163]

Table 5.24. Genotype 2 patients – overall and in subgroups[154,163,164]

Study	Treatment combination	Previous treatment	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Mix	22	23	95.7 (78.1-99.9)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	No cirrhosis	9	9	100 (66.4-100)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Cirrhosis	13	14	92.9 (66.1-99.8)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Mix	Mix	15	16	93.8 (69.8- 99.8)
Dore	daclatasvir for 16 weeks + PR for 16 or 24 weeks RGT	Naive	No cirrhosis	21	24	87.5 (67.6-97.3)
Dore	daclatasvir for 16 weeks + PR for 16 or 24 weeks RGT	Naive	No cirrhosis	19	23	82.6 (61.2-95)
Dore	PR for 24 weeks	Naive	No cirrhosis	17	24	70.8 (48.9-87.4)

CI = confidence interval; DCV = daclatasvir; LL = lower limit; PR = pegylated interferon and ribavirin; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit

Table 5.25. Genotype 3 patients – overall and in subgroups[154,163,164]

Study	Treatment combination	Previous treatment	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Mix	20	24	83.3 (62.6-95.3)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	No cirrhosis	10	12	83.3 (51.6-97.9)
Lawitz 2015	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Cirrhosis	10	12	83.3 (51.6-97.9)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Mix	Mix	168	181	92.8 (88-96.1)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Naive	Mix	89	94	94.7 (88-96.1)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Naive	No cirrhosis	68	71	95.8 (88.1-99.1)

BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Naive	Cirrhosis	21	23	91.3 (72-98.9)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Mix	79	87	90.8 (82.7-95.9)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	No cirrhosis	49	52	94.2 (84.1-98.8)
BOSON	sofosbuvir for 12 weeks + PR for 12 weeks	Experienced	Cirrhosis	30	35	85.7 (69.7-95.2)
Dore	daclatasvir for 12 weeks + PR for 12 or 24 weeks RGT	Naive	Mix	18	26	69.2 (48.2-85.7)
Dore	daclatasvir for 16 weeks + PR for 16 or 24 weeks RGT	Naive	Mix	21	27	77.8 (57.7-91.4)
Dore	PR for 24 weeks	Naive	Mix	14	27	51.9 (31.9-71.3)

Abbreviations: CI = confidence interval; DCV = daclatasvir; LL = lower limit; PR = pegylated interferon and ribavirin; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit

Table 5.26. Genotype 4 patients – overall and in subgroups[165,166]

Study	Treatment combination	Previous treatment	Fibrosis status	Other	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
COMMAND -1	20mg daclatasvir for 12 weeks + PR for 12 weeks	Naive	Mix	SVR24	8	12	66.7 (34.9-90.1)
COMMAND -1	60mg daclatasvir for 12 weeks + PR for 12 weeks	Naive	Mix	SVR24	12	12	100 (73.5-100)
RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Mix	Mix		70	107	65.4 (55.6-74.4)
RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Naive	Mix		29	35	82.9 (66.4-93.4)
RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Experienced	Cirrhosis	Relapser	19	22	86.4 (65.1-97.1)
RESTORE	simeprevir for 12 weeks + PR for 48 weeks	Experienced	Cirrhosis	Non-Relapser	22	50	44 (30-58.1)
RESTORE	simeprevir for 12 weeks + PR for 24 or 48 weeks RGT	Experienced	Cirrhosis		13	28	46.4 (27.5-66.1)

Abbreviations: CI = confidence interval; DCV = daclatasvir; LL = lower limit; PR = pegylated interferon and ribavirin; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit

During the public consultation phase, the company Gilead requested to add this information :“Results of OSIRIS show that SIM+SOF for 12 weeks in patients with G4 is generally safe and well tolerated, with high SVR rates of 95% to 100%” We were not in the possibility to verify this information.

Genotype 5 and 6

There is only very limited information available for genotypes 5 and 6. Five patients with genotype 6 were treated with sofosbuvir + PR for 24 weeks, all achieved SVR24 in the ATOMIC study.[167] In the NEUTRINO study one single patient with genotype 5 and all six patients with genotype 6 in this trial had a sustained virologic response on sofosbuvir + PR.[156]

Special populations

Table 5.27. SVR12 and confidence interval in HCV- and HIV-coinfected patients[164,168-175]

Study	Treatment combination	Duration of treatment (weeks)	Genotype	Previous Treatment Status	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
Onusini	ledipasvir + sofosbuvir	12	1	Both	Mix	49	50	98 (89.4-99.9)
PHOTON-2	sofosbuvir + ribavirin	24	1	Naive	Mix	95	112	84.8 (76.8-90.9)
PHOTON-2	sofosbuvir + ribavirin	12	2	Naive	Mix	17	19	89.5 (66.9-98.7)
PHOTON-2	sofosbuvir + ribavirin	24	2	Experienced	Mix	5	6	83.3 (35.9-99.6)
PHOTON-2	sofosbuvir + ribavirin	24	3	Naive	Mix	52	57	91.2 (80.7-97.1)
PHOTON-2	sofosbuvir + ribavirin	24	3	Experienced	Mix	42	49	85.7 (72.8-94.1)
PHOTON-2	sofosbuvir + ribavirin	24	4	Naive	Mix	26	31	83.9 (66.3-94.5)
Dieterich	simeprevir + PR	12	1	Mix	Mix	78	106	73.6 (64.1-81.7)
Dieterich	simeprevir + PR	12	1	Naive	Mix	42	53	79.2 (65.9-89.2)
Dieterich	simeprevir + PR	12	1	Experienced	Mix	36	53	67.9 (53.7-80.1)
Rodrigo-Torres	sofosbuvir + PR	12	1 to 6	Naive	No cirrhosis	21	23	91.3 (72-98.9)
ION-4	ledipasvir + sofosbuvir	12	1 + 4	Mix	Mix	322	335	96.1 (93.5-97.9)
ION-4	ledipasvir + sofosbuvir	12	1a	Mix	Mix	240	250	96 (92.8-98.1)
ION-4	ledipasvir + sofosbuvir	12	1b	Mix	Mix	74	77	96.1 (89-99.2)
ION-4	ledipasvir + sofosbuvir	12	4	Mix	Mix	8	8	100 (63.1-100)

Study	Treatment combination	Duration of treatment (weeks)	Genotype	Previous Treatment Status	Fibrosis status	Subjects with SVR12 (N)	Subjects studied (N)	SVR12 (95% CI) (%)
ION-4	ledipasvir + sofosbuvir	12	Mix	Mix	No cirrhosis	259	268	96.6 (93.7-98.5)
ION-4	ledipasvir + sofosbuvir	12	Mix	Mix	Cirrhosis	63	67	94 (85.4-98.3)
ION-4	ledipasvir + sofosbuvir	12	Mix	Naive	Mix	143	150	95.3 (90.6-98.1)
ION-4	ledipasvir + sofosbuvir	12	Mix	Experienced	Mix	179	185	96.8 (93.1-98.8)
ALLY-2	sofosbuvir + daclatasvir	12	1 to 6	Naive	Mix	98	101	97 (91.6-99.4)
ALLY-2	sofosbuvir + daclatasvir (NE)	8	1 to 6	Naive	Mix	38	50	76 (61.8-86.9)
ALLY-2	sofosbuvir + daclatasvir	12	1 to 6	Experienced	Mix	51	52	98.1 (89.7-100)
ALLY-2	sofosbuvir + daclatasvir	12	1	Naive	Mix	80	83	96.4 (89.8-99.2)
ALLY-2	sofosbuvir + daclatasvir (NE)	8	1	Naive	Mix	31	41	75.6 (59.7-87.6)
ALLY-2	sofosbuvir + daclatasvir	12	1	Experienced	Mix	43	44	97.7 (88-99.9)
TURQUOISE-1	OBV/PTV/r + DSV + ribavirin	12	1	Mix	Mix	29	31	93.5 (78.6-99.2)
TURQUOISE-1	OBV/PTV/r + DSV + ribavirin	24	1	Mix	Mix	29	32	90.6 (75-98)
PHOTON-1	sofosbuvir + ribavirin	24	1	Naive	Mix	87	114	76.3 (67.4-83.8)
PHOTON-1	sofosbuvir + daclatasvir	12	2 + 3	Naive	Mix	51	68	75 (63-84.7)
PHOTON-1	sofosbuvir + daclatasvir	24	2 + 3	Experienced	Mix	38	41	92.7 (80.1-98.5)

Abbreviations: CI = confidence interval; DSV = dasabuvir; DCV = daclatasvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; PR = pegylated interferon and ribavirin; R = ribavirin; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit; (NE)=the duration or dose of this arm was not as recommended in the EPAR.

Table 5.28. SVR12 and confidence interval in pre- and post-transplantation patients[176-181]

Study	Treatment combination	Duration of treatment	Genotype	Previous Treatment	Fibrosis status	Other	Subjects with	Subjects studied	SVR12 (95% CI)

		(weeks)		Status			SVR12 (N)	(N)	(%)
CORAL-I	OBV/PTV/r + DSV	24	1	Both	No cirrhosis	Post-transplant	33	34	97.1 (84.7-99.9)
Punzalan 2015	simeprevir + sofosbuvir	12	1	Mix	Mix	Post-transplant	40	44	90.9 (78.3-97.5)
Pungapong 2015	simeprevir + sofosbuvir	12	1	Mix	Mix	Post-transplant	94	105	89,5 (82,0-94,7)
SOLAR 1	ledipasvir + sofosbuvir	12	Mix	Mix	Cirrhosis	Pre-transplant	45	52	86.5 (74.2-94.4)
SOLAR 1	ledipasvir + sofosbuvir	24	Mix	Mix	Cirrhosis	Pre-transplant	44	50	88 (75.7-95.5)
SOLAR 1	ledipasvir + sofosbuvir	12	Mix	Mix	Cirrhosis	Post-transplant	100	107	93.5 (87-97.3)
SOLAR 1	ledipasvir + sofosbuvir	24	Mix	Mix	Cirrhosis	Post-transplant	102	107	95.3 (89.4-98.5)
Charlton	sofosbuvir + ribavirin	24	Mix	Mix	Cirrhosis	Post-transplant	28	40	70.0. (53.5-83.4)
Curry	sofosbuvir + ribavirin	prophylactic	Mix	Mix	Cirrhosis	Pre-transplant	30	43	69,8 (53,9-82,8)

Abbreviations: CI = confidence interval; DSV = dasabuvir; LDV = ledipasvir; LL = lower limit; OBV = ombitasvir; PTV = paritaprevir; RIT = ritonavir; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; UL = upper limit

Lalezari et al. reported a SVR12 of 37/38 (97,4%, CI 86,2% to 99,9%) for the treatment of HCV genotype 1-infected patients on methadone or buprenorphine with ombitasvir/paritaprevir/r and dasabuvir plus ribavirin[182].

SVR12 rates were similar in HIV-infected patients and non-HIV-infected patients. SVR12 rates were also similar in pre- and post-transplantation patients, in the few studies on this topic.

Long term outcomes, including mortality and long term relapses

There is no direct evidence on the outcomes of mortality or long-term relapses, as studies had a short follow-up period. The effect of treatment on these outcomes can only be extrapolated from the indirect evidence of a residual disease progression, as observed for treatments that have been on the market for a longer period. This will be further elaborated in the discussion.

Patient reported outcomes.

Patient reported outcomes were collected separately during trials, data collection using specially designed questionnaires was done in surveys that were not part of the trial, and results were reported in separate publications for different studies combined. Multivariate analysis was then used to make comparisons between studies.

Data were collected on participants in the FUSION and NEUTRINO trials and then compared with multivariate analysis. HCV-specific Quality of Life (Chronic Liver Disease Questionnaire-HCV version [CLDQ-HCV]), Functional Assessment of Chronic Illness Therapy-Fatigue, and Work Productivity and Activity Index: Specific Health Problem questionnaires were completed before, during, and after treatment of patients infected with HCV genotypes 2 or 3 who received sofosbuvir and ribavirin for 16 or 12 weeks (the FUSION study, n = 201) or patients infected with HCV genotype 1 who received pegylated interferon, sofosbuvir, and ribavirin for 12 weeks (the NEUTRINO study, n = 327). Patients in each group of the FUSION study had similar PRO and WP scores at each time point (all comparisons, P>0.05). Compared with baseline, patients had modest reductions in fatigue, HCV-

specific quality of life, and WP and Activity Index scores during treatment (P=0.02 to <0.0001). However, by 4 weeks after treatment, all scores returned to baseline levels or higher. Subjects in the NEUTRINO study had greater reductions in these scores during treatment; most remained significant through 4 weeks after treatment (P<0.05). Significant improvements in PROs were observed among patients with sustained virologic responses 12 weeks after treatment in the FUSION and NEUTRINO studies (all P<0.05). In multivariate analyses after adjustment for confounders, interferon therapy was independently associated with worse PROs after 12 weeks of treatment.[183]

In a survey attached to the VALENCE trial, four PRO questionnaires (Short Form-36 [SF-36], Chronic Liver Disease Questionnaire-HCV [CLDQ-HCV], Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F], Work Productivity and Activity Index: Specific Health Problem [WPAI:SHP]) were administered at baseline, end-of-treatment and post-treatment to 334 HCV genotype 2 and 3 patients (naive or treatment-experienced) enrolled in the VALENCE study. Of these, 250 genotype 3 patients were treated for 24 weeks while 73 genotype 2 and 11 genotype 3 patients received 12 weeks of treatment. Throughout and after treatment, patients receiving 12 or 24 weeks had similar FACIT-F, CLDQ-HCV, SF-36 and WPAI:SHP scores (all p >0.05). Compared to their own baseline scores, patients receiving SOF + RBV experienced modest declines in some aspects of SF-36, CLDQ-HCV, fatigue and WPAI:SHP scores (p = 0.04 to <0.0001). By follow-up week 12, all PRO scores returned to the pre-treatment levels (p >0.05). In patients achieving SVR-12 (regardless of the regimen), significant improvements were noted in general health (P=0.0004), CLDQ-HCV (P<0.0001), fatigue (P=0.005), emotional well-being (P<0.0001) and physical component summary score of SF-36 (P=0.0022).[184]

Data from the same surveys attached to the FUSION, the NEUTRINO, and the VALENCE trials were presented separately for patients with cirrhosis. The same four PRO questionnaires mentioned above were administered to subjects from the FUSION trial, (34% cirrhosis), VALENCE trial (21% cirrhosis) and the NEUTRINO trial (17% cirrhosis). During treatment, patients with cirrhosis treated with the IFN-free regimen experienced moderate decline in their PRO scores (0.6%-5.2% on a normalized scale of the summary scores; all P>0.02). In contrast, patients with cirrhosis treated with IFN-containing regimen showed decline in PRO scores that ranged from 3.4% to 16.0% (all P<0.005).[185]

The effect of treatment with sofosbuvir and ribavirin on patient-reported outcomes (PROs) in individuals with HIV/HCV coinfection was also assessed in a survey attached to the PHOTON-1 and PHOTON-2 clinical trials. HIV/HCV-coinfected patients were treated for 12 or 24 weeks with sofosbuvir and ribavirin. Matched HCV-monoinfected controls were also evaluated. All subjects completed the 4 standard PRO questionnaires mentioned above before, during, and after treatment. Included were 497 participants from the PHOTON-1 and PHOTON-2 clinical trials. HCV-monoinfected controls were identified from 2 registered trials, FUSION and VALENCE and used for comparison. At baseline, more impairment in PRO scores was noted in HIV/HCV-coinfected patients, compared with HCV-monoinfected patients. During treatment, moderate decrements in PRO scores (change, up to −6.8% on a 0%–100% scale; P=0.0053) were experienced regardless of treatment duration and were similar to those for HCV-monoinfected patients (all P>0.05). In 413 HIV/HCV-coinfected patients with a virologic response sustained for 12 weeks after treatment cessation, most PRO scores improved (change, up to +7.6%; P<0.0001), similar to findings for HCV-monoinfected patients. In multivariate analysis, in addition to clinical-demographic predictors, coinfection with HIV was associated with PRO impairment at baseline (beta, up to −7.6%; P<0.002) but not with treatment-emergent changes in PRO scores (all P>0.05).[186]

The same four were administered at baseline, during, and after treatment with sofosbuvir + ledipasvir + ribavirin or sofosbuvir + ledipasvir (ION-1,2,3 clinical trials). There were 1005 patients included (stage F0: n = 94; F1: n = 311; F2: n = 301; F3: n = 197; F4: n = 102). At baseline, patients with more advanced fibrosis had more HRQL impairments, predominantly related to physical functioning (stage 0 vs. stage 4 by up to 0.126 on a normalized 0–1 scale P<0.0001). During and post-treatment, HRQoL remained lower in patients with advanced fibrosis. After achieving sustained virologic response, significant improvements from baseline in most HRQL domains were observed regardless of fibrosis stage (by 0.024– 0.103 on a 0–1 scale; all P>0.05 across fibrosis stages). In multivariate analysis, advanced fibrosis was independently associated with impairment of HRQL and work productivity (beta up to 0.056 in comparison with none-to-mild fibrosis, P<0.05). However, improvement of HRQL and work productivity after viral clearance was not related to the stage of fibrosis (all P>0.05). They concluded that although advanced hepatic fibrosis is associated with HRQoL and work productivity impairment, viral eradication with sofosbuvir + ledipasvir leads to HRQoL improvement regardless of

fibrosis stage. HCV patients with early fibrosis experience similar improvement of patient reported outcomes as those with advanced fibrosis.[187]

5.3. Discussion

Summary of main findings

IFN-free combinations

Genotype 1

Treatment-naive patients without cirrhosis, or treatment regimens containing more than one DAA (LDV/SOF12, OBV/PTV/r+DSV12+RBV12, SOF+DCV12, SOF+SMV12), have SVR12 rates above 95%. Differences exist in point estimates, but the studies do not have the power to prove that SVR12 rates are statistically different between treatments; furthermore, there are no direct comparisons between them.

In treatment-naive patients with cirrhosis, the results show a tendency towards lower SVR12 rates compared to non-cirrhotic patients, although not statistically significantly different. All combinations have at least one study arm with a 95% CI that did not include a SVR of 75%. Some study arms have small numbers but their results do not contradict the results of the larger study arms.

Overall, the results for treatment-experienced patients show a larger variability compared to the results for treatment nave patients. All RBV-containing combinations have at least one study arm with a 95% CI that did not include 75%.

Genotypes 2, 3, and 4

For genotype 2 patients, studies on SOF+RBV show SVR12 rates ranging from 86% to 100%. In all but one small arm the 95% CI did not include 70%.

For genotype 3 patients, there is evidence only for the combinations SOF+RBV and SOF+DCV. SVR12 rates are variable, with a tendency towards better results in treatment-naive and non-cirrhotic patients, although there is no evidence that these differences are statistically significant.

For genotype 4 patients, the combination OBV/PTV/r12 excluding DSV, but with RBV, shows a SVR12 rate of 100%, with the 95% CI not including 90%. Evidence for SOF+RBV is mixed, showing a tendency towards lower SVR12 rates, with lower limits of the 95% CI under 50%. Only one small study was found for LDV/SOF, showing a SVR12 rate of 95%, with the lower 95% CI not including 75%.

IFN-containing combinations

Genotype 1

There is evidence from a meta-analysis that SVR12 rates are superior for combinations of SMV+PR or SOF+PR compared with PR alone. There are no significant differences between the new PR-based combinations. There is one study comparing SMV+PR with telaprevir+PR, with subgroup analysis of genotype subtype and cirrhotic state[162]. SVR12 rates were similar in both groups.

Genotypes 2, 3 and 4

Results for the combinations of SMV+PR, SOF+PR, and DCV+PR in other genotypes are limited and mixed. The 95% CI for the treatment arms do not include a SVR12 rate of 50%.

Special groups

Results for HIV-coinfected patients and pre- and post-transplantation patients are similar to those of the other patients.

Strengths and limitation of the review

The report is based on a comprehensive search, and a project plan was prepublished. The main weakness is the fact that only studies with at least one arm containing a new DAA that was subject of

the review were included. As the single-arm studies and RCTs did not have older combinations as a control, we have not assessed their efficacy in a systematic way.

Body of evidence and the reasons why we did not do a network meta-analysis

In the body of evidence, there is a lack of direct comparisons between the newer combinations, both among different molecules and comparisons with older treatments, mainly IFN-containing combinations. Studies are either single-arm studies or randomised studies that compare different durations of treatment of the same combination of molecules, or combinations with and without RBV. Pooling unadjusted single-arm studies is not recommended, as confounding is not handled in an appropriate way; to make proper adjustments using statistical methods such as logistic regression, individual-based data would be needed. Moreover, these adjustments would only address the problem of confounding due to factors that were measured in the studies. Problems such as selection bias and information bias cannot be solved by statistical adjustments, and they are likely to play an important role in a setting where treatment duration is long, side effects – especially in the IFN-containing studies – are important, and where results depend on compliant intake of drugs. This implies also that, even if we had the individual-based data and (always partial) information on a number of confounders, these adjusted comparisons of single-arm studies do not necessarily lead to a more valid estimation of the comparisons between treatments.

Therefore, our position is that lack of a common comparator makes a NMA impossible or at least very unsafe. Innovative approaches, such as selecting arms based on similarities in identified confounding factors, using individual-based data to adjust for confounders, or a mix of these approaches, artificially create randomised controlled trials out of what in reality are only single arm trials. This violates the basic ideas and assumptions underpinning network analysis – a recent methodology where the results of different RCTs, where all biases are addressed by the randomisation procedure, are combined, using the assumption that both intervention and control arms are sufficiently similar to have an acceptable transferability of the treatment effects over the study arms.

Moreover, it is doubtful that existing evidence from the studies has a sufficient sample size to demonstrate or exclude a clinically important difference in a non-inferiority analysis, given the high SVR rates observed for therapies combining different second-generation DAAs.

Quality of the studies

Studies were either single-arm studies or RCTs where the randomisation was not relevant to our research question, because they randomised the same regimen with or without RBV and, in some cases, different treatment durations. Therefore, we quoted allocation concealment and random sequence generation as non-applicable in these cases. A randomised, open-label study comparing a pegylated interferon (Peg-IFN)-containing regimen to an IFN-free combination is not always easy to conduct. In one case, a drop-out rate of 23% before the start of treatment in the Peg-IFN combination arm was remarkable[153]. Most studies were open-label studies. Whereas this did not create a high risk of bias for SVR rates, it may have introduced bias in the reporting of side effects, e.g. in one study that was blinded and where a placebo control group was included for the 12-week treatment duration (patients allocated to the placebo group received effective treatment immediately after the 12 weeks duration), considerable side effects were attributed to the placebo control group[145]. This study set up has considerably less risk of bias, but was unfortunately not common.

The large majority of the studies were industry-sponsored, where conduct, analysis of data, and reporting was controlled by the industry. A Cochrane review concluded that sponsorship of drug and device studies by the manufacturing company leads to more favourable results and conclusions than sponsorship by other sources. Their analyses suggest the existence of an industry bias that cannot be explained by standard “risk of bias” assessments[188]. It is unclear, however, to what degree these findings also apply to the studies included in our review and if this constitutes a high risk of bias.

Some studies were single-centre studies conducted in the US, such as the studies by Osinusi[147] and Ruane[161]. Some were conducted in Japanese patients[143,157]. These factors may limit applicability in the European context.

Different treatment durations and the use of ribavirin

There is still considerable uncertainty on the optimal treatment duration and on the need to add RBV to the treatment, despite the fact that studies randomised for these factors.

Moreover, in the RCTs that did randomise different treatment durations or the addition of RBV, they did not report the effect measures (such a odds ratio or risk ratio) for these comparisons but only proportions per treatment arm or, if they did, this comparison was not the primary objective of the study. Analysis was mostly limited to calculating SVR rates with corresponding exact confidence CIs. The studies that had as a stated objective to prove non-inferiority were only powered to demonstrate differences of 15% between groups, and smaller differences may be clinically important.

Cirrhotic patients and treatment-experienced patients

Although data suggest that SVR rates are reduced in cirrhotic and treatment-experienced patients for certain combinations, this reduction is not always present, and 95% CIs are too wide to show statistical evidence of this reduction.

Clinically relevant outcomes

How sustained is SVR?

Therapy combinations based on Peg-IFN-alfa have, with increasing success, been able to lower HCV-RNA in a sustained way to levels not detectable using standard assays (SVR at 12 or 24 weeks after treatment end). Also note that some study protocols consider the (rare) patient who still has a very low level of viral RNA in plasma (below the validated range of measurement) as a patient with SVR.

SVR12 has replaced SVR24 as the primary efficacy endpoint for phase II and III clinical trials evaluating new antiviral treatments of CHC, making the trials shorter and less costly. Only a low proportion of patients will relapse after SVR12 or SVR24. For example, in one study, 5 years following IFN-containing treatment, 4.7% (95% CI 2.0 to 7.4) had a relapse after SVR24[189]. After SVR12, this proportion is likely to be 2% higher compared with SVR24[190]. If, for a specific treatment, the SVR12 rate is 95%, it could be that the real rate of failure after a few years is not 5% but over 10%. To date, there are no long-term data available on the frequency of relapse after SVR12 following the new hepatitis C combinations administered in a real-life setting. In addition, further research is needed to explore any harms caused by very low levels of HCV that may remain present in some patients and that go undetectable using standard plasma-based HCV-RNA tests[113].

SVR after Peg-IFN-containing treatments in a real-life setting is low

Because of tolerability issues, co-morbidities excluding patients from treatment or a lack of insurance coverage, the uptake of IFN-containing treatment combinations has remained relatively low. For example, only a third of US patients infected with HCV were candidates for Peg-IFN-containing treatment. Furthermore, patients for whom Peg-IFN was suitable might have elected not to pursue treatment to avoid potential side effects. Overall, less than 5% to 6% of infected patients had achieved SVR in the US (as reported in 2013)[191].

It can be expected that treatment combinations that are better tolerated will look more attractive to a broader population of chronically infected patients.

Long-term benefits of treatment versus no treatment are not well known

An increased incidence of liver cirrhosis and HCC are well known effects of a chronic HCV infection. Also, other types of cancer (pancreas, rectum, kidney, non-Hodgkin's lymphoma, and lung) are seen more frequently[110].

Whereas it is clear that patients who achieved SVR after IFN-containing treatment show much less disease progression compared with patients who did not achieve SVR, it should be clear that such responder analysis is not a valid proof of treatment benefit. However, many health-economic models are based on long-term studies comparing outcomes of patients with SVR (responders) with non-responders or natural history data obtained in populations that have more co-factors than those

patients eligible for IFN-containing treatment. This clearly leads to an overestimation of the treatment effect.

RCTs that are informative about the overall effect of treatment versus no treatment on the incidence of liver cirrhosis, HCC, or mortality are scarce[192,193]. Only the HALT-C and the EPIC trials were of good quality and compared a long-term, low-dose Peg-IFN (a non-standard treatment regimen for chronic hepatitis C) versus watchful waiting. These two studies included 1676 patients. Both studied patients with severe fibrosis (demonstrated on liver biopsy) and were designed to assess the clinical outcomes. The study population consisted of patients who had failed a previous treatment, thus the treated arms had low SVR rates (under 20%). Surprisingly, a somewhat higher overall mortality rate was seen in the treated arms, and no support was found in these trials for SVR as a surrogate marker.

What we can learn from the analysis of patients with SVR after IFN-containing treatment is that, in about half of the patients with liver fibrosis and SVR, some form of regression of the fibrosis stage is seen and progression to liver cirrhosis is rare in the absence of other factors leading to cirrhosis. Also, portal pressure is reduced. Patients with SVR, however, remain at risk of HCC, especially patients with cirrhosis. Long-term follow-up studies indicated that SVR was associated with not only a reduced occurrence of solid clinical endpoints, including liver failure and HCC, but also cardiovascular events and malignant lymphomas[189,194,195].

Reductions in risk of progression after treatment are often overestimated, as data are not adjusted for co-factors present in a real-life population

The question remains whether the excellent long-term outcome of the patients eligible for IFN treatment and who achieved SVR are representative of the outcome after SVR of a more broad patient population that is eligible for the new treatment combinations (assuming the new treatments become affordable). Most probably, the broad population treated with the new drugs will have more co-factors that, independently from the chronic HCV infection, may continue to drive the process towards liver cirrhosis and HCC. Therefore, reductions in the risk of disease progression are expected to be lower.

Table 5.29. Factors independently related to rapid fibrosis progression rate[a] in 267 patients with untreated CHC of known duration (copied from Mallat[196])

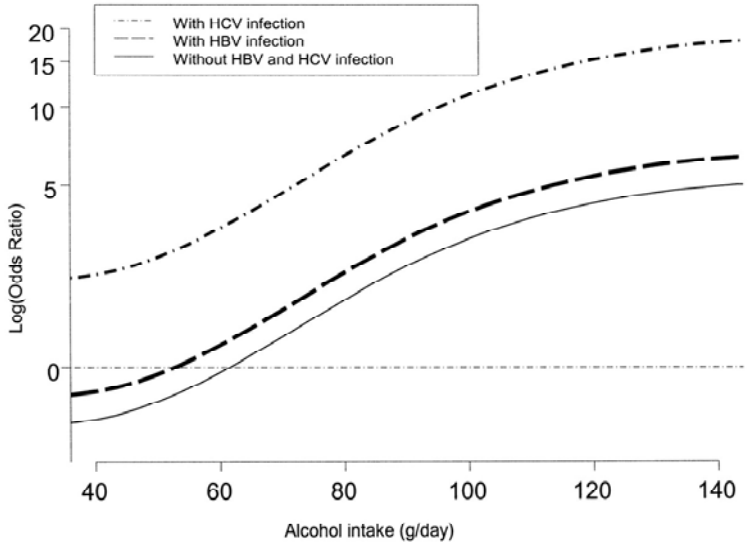
	FPR > 0.074 (U/year) (%)	OR (95% CI)	P-value
Disease-time cannabis use			
None	39.7	reference	-
Occasional	42.5	1.3 (0.5-3.3)	0.57
Daily	68.5	3.4 (1.5-7.4)	0.005
Age at contamination			
<= 20 years	41.4	reference	-
21-40 years	52.9	2.4 (1.2-4.8)	0.01
> 40 years	70	10.5 (3.0-37.1)	<0.001
Metavir activity grade			
<A2	25.9	reference	-
>=A2	67.5	5.4 (2.9-10.3)	<0.001
HCV genotypes			
1	42	reference	-

	FPR > 0.074 (U/year) (%)	OR (95% CI)	P-value
2	35	1.0 (0.3-3.1)	0.95
3	74.2	3.4 (1.5-7.7)	0.005
4/5	45.8	1.2 (0.4-3.6)	0.69
Disease-time alcohol intake			
< 30 g/day	42.1	reference	-
>=30 g/day	69.3	2.2 (1.1-4.5)	0.03
Staetosis			
Absent-mild	40.7	reference	-
Moderate-severe	72.4	2 (1-4.1)	0.05

a As defined by fibrosis progression rate >0.076 Metavir U/year (median value of the cohort).

Co-factors include alcohol use, cannabis use, steatosis and smoking, the latter through increased activation of inflammation in the liver[196].

Figure 5.1. Risk of HCC by alcohol intake and infection with HBV or HCV (copied from Donato[87])



HCC risk is not only high in HCV-infected individuals but may be even higher in heavy drinkers compared with those with chronic HCV infection[87].

Data from the US hint to the importance of co-factors. For example, 10 years after a documented seroconversion, liver cirrhosis was seen in 18.4% of infected individuals versus 6.1% of non-HCV-infected individuals, in a US veterans affairs (VA) study that had cases and controls matched for age, sex, and race[197].

In theory, eliminating HCV as a contributing factor could reduce the incidence of cirrhosis to a level that can be explained by other factors. For example, in the VA study population, this reduction could theoretically be from 18.4% to 6.1%. (In contrast, most health economic models include a reduction to 0% progression to cirrhosis after SVR, which can only be considered appropriate if patients with co-factors are fully excluded from treatment.)

A broader analysis of the VA indicates that SVR is associated with a hazard ratio of 0.62 for the development of liver cirrhosis and for HCC[85].

Rates in cause-specific mortality among people diagnosed with HCV in 3 regions with well-established population-based HCV diagnosis databases (Scotland, United Kingdom; New South Wales, Australia; and British Columbia, Canada) show liver-related deaths accounted for 21% to 26% of deaths. Liver cancer was followed by alcoholic liver disease (mortality was very high in Scotland) and non-alcohol liver disease as the reported cause of death. In this population, over three-quarters of deaths in each region were due to non-liver related causes. Drug-related mortality was about equally important as mortality related to liver disease. The proportion of the population treated each year had increased to 2% to 3%, but no treatment effect was detectable on population mortality level[72].

The fact that alcoholic liver disease is more important (Scotland) or about equally important as a cause of death as non-alcohol liver disease (which could be decreased by successful antiviral treatment) and the high burden of drug-related mortality suggest that, even after SVR, the mortality rates will remain higher than average.

In conclusion, all available evidence suggests that obtaining SVR has beneficial effects for chronic hepatitis C patients with regards to morbidity and probably also mortality. The extent of the long-term benefit is however not well documented. Compared with Peg-IFN-containing combinations, a broader range of patients are eligible for IFN-free treatment and are willing to be treated. It is important that treating physicians also consider co-factors such as alcohol use, because the residual risk of liver disease progression after SVR is mainly determined by such co-factors.

6 SAFETY

6.1. Research questions

Element ID	Research question
C0008	a) How do the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) affect the frequency and type of adverse events in relation to the comparators and to each other? b) How do the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) affect the frequency and type of serious adverse events in relation to the comparators and to each other?
C0002	Are the harms related to dosage or frequency or administration of the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in relation to the comparators and to each other?
C0004	How does the frequency or severity of harms change over time or in different settings of the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in relation to the comparators and to each other?
C0005	What are the susceptible patient groups that are more likely to be harmed with the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in relation to the comparators and to each other?
B0010	What kind of data/records and/or registry is needed to monitor the use of the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) and the comparators?

6.2. Results

Patient safety

[C0008 a] How do the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) affect the frequency and type of adverse events in relation to the comparators and to each other?

[C0008 b] How do the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) affect the frequency and type of serious adverse events in relation to the comparators and to each other?

In the HTA Core Model, the Safety Domains section describes the direct and indirect harms of a technology for patients, staff, and the environment, as well as how to reduce the risk of harms[198]. The harmful effects of a technology are essential in quantifying the net benefit (benefit minus harms) of an intervention. The harms are identified, quantified in terms of frequency, incidence, severity, and seriousness, and finally compared to those of the comparator(s)[199].

The aim of this relative safety assessment was to determine whether treatment with 6 new oral direct-acting antivirals (DAAs) (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in adults with chronic HCV infection is safer than treatment with their comparators (the first generation of DAAs, telaprevir and boceprevir, and an interferon-ribavirin regimen) and to each other. More specifically, our primary outcomes were the frequency of adverse

events (AEs), including any AEs, serious AEs (SAEs), most frequent AEs, and discontinuations due to AEs.

For the relative safety assessment, we planned to find and update recent, high-quality systematic reviews (SRs) with the PICO (Patient-Intervention-Comparison-Outcome) scheme relevant for this assessment. Whitlock[200] and Robinson[201] assessed how to integrate existing SRs into new SRs; they found that consensus among systematic review organisations and the Evidence-based Practice Centres (EPCs) regarding some aspects of incorporating existing SRs already exists, but areas of uncertainty remain: how to synthesize, grade the strength of, and present bodies of evidence composed of primary studies and existing SRs. Use of existing SRs may include: (1) using the existing SR(s)' listing of included studies as a quality check for the literature search and screening strategy conducted for the new review (Scan References); (2) using the existing SR(s) to completely or partially provide the body of included studies for one or more Key Questions in the new review (Use Existing Search); (3) using the data abstraction, risk of bias assessments, and/or analyses from existing SRs for one or more Key Questions in the new review (Use Data Abstraction/Syntheses); or (4) using the existing SR(s), including conclusions, to fully or partially answer one or more Key Questions in the new review (Use Complete Review).

As mentioned above, Whitlock[200] and Robinson[201] methodology was used to integrate existing SRs into a new SR. We were able to update one recently published SRs related to genotype 1 HCV infection, namely on simeprevir (SMV) and sofosbuvir (SOF), each in combination with pegylated interferon and ribavirin (PR)[13].

Quantitative synthesis from existing SRs was used and presented in the Results section only for SMV and SOF, each in combination with PR, for genotype 1 HCV infection.

Quantitative synthesis of safety data in our new SR using meta-analysis was not possible, nor for interferon-containing regimens nor for interferon-free regimens. The results are presented in plain text format, supplemented by overview tables. In Appendix 1 we present details of the studies included for the Safety Domain, evidence tables, and risk of bias tables according to the Cochrane Collaboration risk of bias tool[14].

Interferon-containing regimens for genotype 1 HCV infection

The assessment of both simeprevir (SMV) and sofosbuvir (SOF) in combination with PR for genotype 1 HCV infection was based on a SR including network meta-analysis (NMA), published in October 2014 by the Canadian Agency for Drugs and Technologies in Health[13] and it updates with data from recently published clinical studies.[153,162,168]

Short summary of the Canadian SR[13]

The results of the Canadian SR for both treatment regimens are summarised briefly below. In total, 5 individual trials of SMV+PR and 3 individual trials of SOF+PR were included. Appendix 1 shows an overview of included studies for both treatment-naive and treatment-experienced patient populations.

The patients enrolled were adults with genotype 1 chronic HCV infection, excluding patients with decompensated liver disease, HIV coinfection, and other causes of liver disease. The outcomes reported included sustained virological response at 12 weeks (SVR12) or sustained virological response at 24 weeks (SVR24), treatment completion, virological relapse, mortality, health-related quality of life, and AEs. None of the studies reported histological changes, liver failure, hepatocellular carcinoma, or need for liver transplant.

SMV+PR

In total, 5 individual studies were included in the Canadian SR, 3 in treatment-naive patients with a total of 1,171 patients (PILLAR, QUEST-1, and QUEST-2) and 2 in treatment-experienced patients with a total of 855 patients (ASPIRE and PROMISE). Treatment-experienced patients were either relapsers (ASPIRE and PROMISE), or partial or null responders to previous PR therapy (ASPIRE); the criteria used to define relapse were similar across the 2 studies. All 5 studies compared SMV+PR with PR therapy + placebo over 48 weeks of treatment, and all were included in the NMA.

SOF+PR

Overall, 3 individual studies were included in the Canadian SR, all of which were in treatment-naive patients (PROTON, ATOMIC, and NEUTRINO). Of these, 1 study of 121 patients that compared SOF+PR with PR therapy + placebo over 48 weeks of treatment was included in the NMA (PROTON). The 2 remaining studies (ATOMIC and NEUTRINO) with a total of 643 patients could not be included in the NMA due to lack of a linking treatment group; ATOMIC included only 1 treatment group that met the dose-related inclusion criteria, and NEUTRINO was a single-arm, uncontrolled trial.

Across both SMV+PR and SOF+PR studies, three key AEs were identified — anaemia, depression, and rash — and were analysed using NMA methods (details can be found in Appendix 1). Regarding SMV, there was no statistically significant difference in the Relative Risk of anaemia, depression, and rash between the SMV-containing treatment groups and the groups receiving PR in either treatment-naive or treatment-experienced patients. In terms of SOF, there was no difference in the Relative Risk of anaemia and rash between the group receiving SOF in combination with PR and the group receiving PR alone in treatment-naive patients; depression was not reported.

The risk of anaemia was not statistically significantly higher for patients who received SMV+PR or SOF+PR versus PR alone, based on both direct pair wise and indirect comparisons.

No statistically significant differences were detected between SMV+PR and PR alone regarding the risk of depression for both treatment-naive and treatment-experienced patients, in both direct and indirect analyses. No comparative data were available for SOF.

No direct or indirect treatment comparisons showed statistically significant differences for rash in treatment-naive patients for SMV or SOF.

No clear increased risk of the other AEs like influenza-like symptoms or neutropenia were observed among patients who received SMV+PR or SOV+PR, compared with PR alone. Suicidal ideation was reported infrequently, and no conclusions can be drawn.

Update of Canadian SR *(data from Reddy[162], Dieterich[168] and Pearlman[153])*

Overall, we identified 3 new studies regarding HCV genotype 1 infection for our update of the Canadian SR (table 6.1.):

- 1 study on SMV+PR in treatment-experienced patients (for details see Appendix 1): Reddy[162] ATTAIN study.
- 1 study on SMV+PR in patients with HIV-coinfection (for details see Appendix 1): Dieterich[168].
- 1 study on SOF+PR in combined (naive-experienced) patients (for details see Appendix 1): Pearlman[153].

Only Reddy[162] ATTAIN study was a head-to-head comparative study and described a comparison of SMV+PR vs telaprevir+PR.

SMV+PR

Although we identified a couple of new studies in *treatment-naive* patients, none of them used SMV at a dose of 150 mg daily, as indicated in the Summary of Product Characteristics (SmPC), but at a lower daily dose of 50 mg to 100 mg [7,12]. Therefore, we haven't included these studies in the update.

In *treatment-experienced* patients, we identified 1study on SMV+PR: Reddy[162] ATTAIN study published a global, randomised, double-blind, double-dummy, active-controlled phase III study in previous non-responders with genotype 1 chronic HCV infection with or without cirrhosis. The objective was to assess whether SMV for 12 weeks + PR for 48 weeks (n=379) is non-inferior in terms of efficacy to telaprevir for 12 weeks + PR for 48 weeks (n=384).

The frequency of any AE was 92% in the SMV group and 97% in the telaprevir group. The study authors reported the most common "AE of interest" as being pruritus (SMV 32% vs telaprevir 44%), any type of rash (21% vs 31%), neutropenia in the SMV group (18%), and anaemia in the telaprevir

group (38%). While in the SMV group 3% of patients discontinued treatment because of an AE, the frequency in the telaprevir group was 10%. SAEs were not reported in detail for either group but occurred in 2% of patients in the SMV group and in 9% of patients in the telaprevir group. Grade 3/4 AEs also occurred less often in the SMV group than in the telaprevir group (23% vs 28%). While no patient receiving SMV died, there was one death in the telaprevir group due to septic shock secondary to bullous erysipelas.

In combined treatment-naive and treatment-experienced patients, no new studies were found which used SMV at a dose of 150 mg daily, as indicated in the Summary of Product Characteristics (SmPC). The few studies identified used SMV at lower daily doses (100 mg) [8] and therefore were not included in the update.

In *patients with HIV-coinfection* we identified 1 study on SMV+PR and included it despite the fact that the Canadian SR excluded patients with HIV coinfection[13].

Dieterich[168] was a multi-country, multi-site, open-label trial that included both treatment-naive and treatment-experienced patients with HCV genotype 1/HIV co-infection with or without cirrhosis. Overall, 106 patients received SMV for 12 weeks+PR: noncirrhotic HCV treatment-naive patients and prior relapsers were treated with PR response-guided therapy until week 24 or 48; prior null responders, prior partial responders, and all patients with cirrhosis irrespective of prior treatment experience received PR until week 48.

In total, 96% of patients experienced any AE, the most common being fatigue (41%), headache (28%), and nausea (26%). About 5% of patients discontinued treatment due to an AE. Almost 6% of patients experienced a SAE (details can be found in Appendix 1), and 33% of patients reported a grade 3/4 AE. There was no death during the study.

SOF+PR

We couldn't find any study assessing the combination of SOF+PR in treatment-naive or treatment-experienced patients. Only in *combined treatment-naive and treatment-experienced patients*, 1 study was found on SOF+PR [153].

Pearlman[153] reported a prospective, randomised, open-label study of 82 patients with genotype 1a chronic HCV infection with cirrhosis; 50 patients (61%) had not responded to treatment with PR (null responders), and 32 patients (39%) were treatment-naive. Patients were assigned randomly to receive either SMV+SOF for 12 weeks (n=62; 58 in final analysis) or SOF+PR for 12 weeks (n=31; 24 in final analysis). Only the latter group is described here.

In the SOF+PR group, the majority of patients reported AEs (91%), and the most frequent were fatigue (71%), headache (33%), and nausea (29%); three patients (13%) discontinued study drugs due to AEs and 1 SAE was reported (moderate ascites). Grade 3/4 AEs were not reported. No patient died during the study.

Table 6.1. summarises any AEs, the most frequent AEs, SAEs and discontinued treatment due to AEs reported with SMV+PR and SOF+PR treatment regimens in patients with genotype 1 HCV infection.

Table 6.1. Any AEs, the most frequent AEs, SAEs, discontinued treatment due AEs with SMV+PR and SOF+PR regimens, in genotype 1 patients[153,162,168]

Drug combination and studies	Any AEs N (%)	The most frequent AEs (%)	SAEs N (%)	Discontinued treatment due AEs n (%)
SMV+PR				
Reddy et al. (2015) ATTAIN study[162] SMV12 + PR48; telaprevir 12 + PR48	347 (92) in SMV+PR group; 371 (97) in telaprevir+PR	pruritus (32), rash (21), neutropenia (18) (in SMV+PR group); pruritus (44), anaemia (38), rash	8 (2) in SMV+PR group; 33 (9) in telaprevir+PR group	12 (3) in SMV+PR group; 39 (10) in telaprevir+PR group

	group	(31) (in telaprevir+PR group)		
In HIV coinfection				
Dieterich et al. (2014)[168]: SMV12+PR24-48 RTG; SMV12+PR48	102 (96.2)	fatigue (40.6), headache (28.3), nausea (25.5)	6 (5.7)	5 (4.7)
SOF+PR				
Pearlman et al. (2015)[153] SOF12 + PR12	22 (91)	fatigue (71), headache (33), nausea (29)	1 (4)	3 (13)

12 = 12 weeks; 24 = 24 weeks; 48 = 48 weeks; AE = adverse event; IFN = interferon; PR = pegylated interferon and ribavirin;SAE= serious adverse event; SMV = simeprevir; SOF = sofosbuvir; RGT = response- guided therapy

In conclusion, the findings for treatment-naive, treatment-experienced, and combined patients on SMV, in combination with PR, for genotype 1 HCV infection were similar in terms of the AEs reported; the overall AE profile in SMV-treated patients in combination with PR was comparable to that in patients who received PR alone. The most frequent AEs in both groups were neutropenia, anaemia, rash, and pyrexia. The rates of discontinuations due to AEs were similar for both the SMV+PR group and the PR alone group; the same was true for SAEs. No new comparative data were available for SOF+PR versus PR alone.

In the only one head-to-head study found, the ATTAIN study, Reddy[162] differences were recorded between treatment groups in SMV- or telaprevir-related AEs (69% in the SMV+PR group vs 86% in the telaprevir+PR group), SAEs (2% vs 9%), and AEs leading to study drug discontinuation (2% vs 8%).

No new comparative data were available for SOF+PR versus PR alone.

A limitation of these studies is that important patient populations were excluded, such as HIV- (except Dieterich[168] on SMV) and hepatitis B virus (HBV)-coinfected patients, liver transplanted patients, and those with decompensated liver disease.

Interferon-containing regimens for genotypes 2 to 6 HCV infection

Data on safety outcomes for interferon-containing regimens (frequency of any AE, most frequent AEs, discontinuations due to AEs, SAEs, deaths, and most frequent SAEs) can be found in detail in Appendix 1, section 1.2 (treatment-naive patients, treatment-experienced patients, and HIV-coinfection). Summary data are listed in Table 6.2. For the group of patients pre- or post-liver transplantation only studies assessing interferon-free regimens could be identified and are reported there.

Treatment-naive patients – AEs

In treatment-naive patients the following studies were identified:

- 1 study on SOF+PR: Gane[1] ELECTRON study (genotype 2 or 3).
- 1 study on DCV+PR: Hezode[165] COMMAND-1 study (genotype 1 or 4).

SOF+PR

Gane[1] ELECTRON study was an open-label, multipart, trial conducted at two centres. Patients with HCV genotype 2 or 3 infection (n=11) without cirrhosis were treated with SOF+PR for 12 weeks. However, this is not an approved regimen for genotype 2 patients, but only for genotype 3 patients. Of the 11 patients included in this study arm, 4 (36%) had a genotype 2 infection and 7 (64%) had a genotype 3 infection.

The frequency of any AE was not reported, however, the most commen AEs were headache (73%), fatigue (45%), and insomnia (45%). There was no SAE. The authors did not report on treatment discontinuations, grade 3/4 AEs, or deaths.

DCV+PR

Hezode[165] COMMAND-1 study was a double-blind, placebo controlled trial in patients with HCV genotype 1 or 4 infection with or without cirrhosis. Patients were randomised into three different treatment groups. In the first group patients received DCV at a dose of 20 mg in combination with PR; because of the low dose of DCV we don't report this group. In the second group, 158 patients received DCV+PR for 24 weeks. Of these, 146 were infected with genotype 1 HCV and 12 were infected with genotype 4 HCV. However, the combination DCV+PR is only approved in patients with genotype 4 HCV infection, which were the minority of patients (8%) in this treatment arm. In the control group (third group) 78 participants received placebo for 24 weeks in combination with PR for 24 or 48 weeks. Of these, 72 had a genotype 1 infection and 6 had a genotype 4 infection. For the reporting of outcomes, the authors merged results for patients with genotype 1 and genotype 4.

The frequency of any AE was not reported. The AE profile in patients treated with DCV+PR was comparable with that observed in patients who received PR alone. The most common AEs in both treatment arms were fatigue (DCV 54% vs placebo 59%), headache (43% vs 46%), and pruritus (40%) in the DCV arm as well as insomnia (39%) in the placebo arm. More patients in the placebo arm than in the DCV arm discontinued treatment (10% vs 4%). SAEs occurred in around 8% of patients in both groups but were not further specified. Grade 3/4 AEs were more often reported in the placebo arm than in the DCV arm, 23% vs 15%. There was no death in either group.

Treatment-experienced patients – AEs

In treatment-experienced patients, the following study was identified:

- 1 study on SOF+PR: Lawitz[163] (genotype 2 or 3).

SOF+PR

Lawitz[163] was a single-site, open-label, uncontrolled study including treatment-experienced patients with HCV genotype 2 or 3 infection with or without cirrhosis; 47 patients received SOF+PR for 12 weeks.

96% of patients had any AE, the most common of which were influenza-like illness (55%), fatigue (32%), and anaemia (30%). 9% of patients discontinued treatment due to an AE. Another 9% of patients had a SAE, including cholecystitis, sepsis, anaemia, decompensated cirrhosis, and esophageal varices haemorrhage. The study authors didn't report grade 3/4 AEs or deaths.

Combined (treatment-naive and treatment-experienced) patients – AEs

In combined (treatment-naive and treatment-experienced) patients, the following studies were identified:

- 1 study on SOF+PR: Foster[154] BOSON study (genotype 2 or 3).
- 1 study on SMV+PR: Moreno[166] RESTORE study (genotype 4)

SOF+PR

Foster[154] BOSON study was a randomised, open-label study conducted at 80 sites in the UK, Australia, the US, Canada, and New Zealand. Patients with HCV genotype 2 infection with cirrhosis and patients with HCV genotype 3 infection with or without cirrhosis were included. They received either SOF+RBV for 16 weeks (n=196), or SOF+RBV for 24 weeks (n=199), or SOF+PR for 12 weeks (n=197). The groups that received the regimens of SOF+RBV are described further below. The regimen of SOF+PR for 12 weeks is only approved for patients with HCV genotype 3 infection but not for those with genotype 2 infection. However, the vast majority of patients in this group (92%) had a genotype 3 infection.

In this study, 99% of patients had any AE, the most common being fatigue (46%), headache (36%), as well as insomnia and nausea (25% each). 1% of patients discontinued treatment due to an AE. SAEs occurred in 6% of patients. The authors only reported SAEs in more than one patient; these included atrial fibrillation, depression, and syncope. 8% of patients had a grade 3/4 AE. No patient died during the study.

SMV+PR

Moreno[166] RESTORE study was a multi-centre, single-arm, open label trial conducted in 8 centres in Belgium and France. Overall, 107 patients with HCV genotype 4 infection with or without cirrhosis received either SMV for 12 weeks in combination with PR response-guided therapy for 24 or 48 weeks (treatment-naive and prior relapsers, n=57) or SMV for 12 weeks in combination with PR for 48 weeks (prior null and partial responders, n=50).

The frequency of AEs was 98%; the most common AEs were influenza-like illness (46%), asthenia (42%), and fatigue (36%). One patient discontinued treatment due to an AE and SAEs occurred in 5 patients (5%); including angina pectoris, bradycardia, diabetes mellitus, hypoglycaemia, anaemia, overdose, and spondylitic myelopathy. Grade 3/4 AEs occurred in 7% of patients; there was no death reported.

HIV coinfection /treatment-naive or treatment-experienced or combined (treatment-naive or treatment-experienced)

The following study was identified in HIV-coinfected patients:

- 1 study on SOF+PR: Rodriguez-Torres[172] Part B (genotype 1 to 4).

SOF+PR

Rodriguez-Torres[172] Part B was a single-site, single-arm, open-label study. Treatment-naive patients with HCV genotype 1 to 6 infection with HIV-coinfection without cirrhosis were treated with SOF+PR for 12 weeks. Of the 23 patients, 15 (65%) had HCV genotype 1a infection, 4 (17%) had HCV genotype 1b infection, 1 (4%) had HCV genotype 2b infection, 2 (9%) had HCV genotype 3a infection, and 1 (4%) had HCV genotype 4 infection. There were no patients with HCV genotype 5 or 6 infection.

70% of patients reported any AE; the most common AEs were blood and lymphatic system disorders (57%), anaemia (52%), and neutropenia (17%). About 9% of patients discontinued treatment due to an AE. There were no SAEs or deaths during the study; grade 3/4 AEs were not reported.

Pre- or post-liver transplantation /treatment-naive, or treatment-experienced, or combined (treatment-naive or treatment-experienced)

No studies were identified assessing interferon-containing regimens in this group of patients.

Table 6.2. summarises any AEs, the most frequent AEs, SAEs and discontinued treatment due to AEs reported with DAAs + PR regimen in genotypes other than genotype 1 and with HIV coinfection.

Table 6.2. Any AEs, the most frequent AEs, SAEs, discontinued treatment due AEs with DAAs under assessment + PR regimen in genotypes other than genotype 1 and with HIV coinfection[1,154,163,165,166,172]

Drug combination and studies	Any AEs N (%)	The most frequent AEs (%)	SAEs N (%)	Discontinued treatment due AEs n (%)
SOF				
With interferon regimen in genotype other than 1				

Gane et al. (2013) [1] ELECTRON study: SOF12+PR12	NR	headache (73), fatigue (45), insomnia (45)	0	NR
Foster et al. (2015)[154] BOSON study: SOF12+PR12	195 (99)	fatigue (46), headache (36) , insomnia (25), nausea (25)	12 (6)	2 (1)
Lawitz et al. (2015) [163]**:** SOF12+PR12	45 (96)	influenza-like illness (55), fatigue (32), anemia (30)	4 (9)	4 (9)
In HIV coinfection and interferon regimen in genotype 1-4				
Rodriguez-Torres et al. (2015)[172] Part B: SOF12+PR12	16 (69.9)	blood and lymphatic system disorders (56.5), anaemia (52.2), neutropenia (17.4)	0	2 (8.6)
SMV				
With Interferon regimen in genotype other than 1				
Moreno et al. (2015) [166] RESTORE study, SMV12+PR24/48 RGT; SMV12+PR48	105 (98.1)	influenza-like illness (45.8), asthenia (42.1), fatigue (34.6)	5 (4.7)	1 (0.9)
DCV				
With Interferon regimen in genotype other than 1				
Hezode et al. (2015)[165] COMMAND-1 study: DCV24+PR24; Placebo24+PR24/48	158; 78	fatigue (54.4), headache (43), pruritus (39.9); fatigue (59), headache (46.2), insomnia (38.5)	13 (8.2); 6 (7.7)	7 (4.4); 8 (10.3)

12 = 12 weeks; 24 = 24 weeks; 48 = 48 weeks; AE = adverse event; DAA = direct-acting antiviral; DCV = daclatasvir; PR = pegylated interferon and ribavirin; RGT = response-guided therapy; SMV = simeprevir; SOF = sofosbuvir

In conclusion, frequency of any AEs reported with three DAAs + PR regimen in genotypes other than genotype 1 (SOF, 4 clinical studies, one with HIV coinfection; SMV and DCV, one study each) was within the range of 70%-99%, SAEs were reported with frequency of 4.7%-9%. The most frequent AEs across all studies were headache, fatigue and insomnia, and in HIV confection patients, anemia and neutropenia (52%-57%).

Interferon-free regimens for genotype 1 to 6 HCV infection

Data on safety outcomes for interferon-free regimens (frequency of any AE, most frequent AEs, discontinuations due to AEs, SAEs, deaths, and most frequent SAEs) can be found in detail in Appendix 1, section 1.2 (treatment-naive patients, treatment-experienced patients, HIV-coinfection and pre- or post-liver transplantation). Summary data are listed in Table 6.3.

Treatment-naive patients – AEs

In treatment-naive patients the following studies were identified:

- 2 studies on SOF+RBV: Osinusi[202] Part 2, and Gane[1] ELECTRON study.
- 4 studies on SOF+LDV with or without RBV: Afdhal[142] ION-1 study, Lawitz[10] LONESTAR study, Cohort A, Kowdley[9] ION-3 study, and Gane[203] ELECTRON study.
- 1 study on DCV+SOF: Sulkowski[2] Group G.
- 1 study on OBV+PAR+RIT with or without RBV: Hezode[204] PEARL-1 study.
- 3 studies (in 2 publications) on OBV+PAR+RIT+DSV with or without RBV: Feld[149] SAPPHIRE-I study, and Ferenci[150] PEARL III and PEARL IV studies.

SOF+RBV

Osinusi[202] was a single-centre, randomised, open-label trial. In part 2 of the trial, 50 participants with HCV genotype 1 and all stages of liver fibrosis were randomised to receive SOF with either weight-based or low dose (600 mg) RBV for 24 weeks.

Gane[1] ELECTRON study was an open-label, multipart, trial conducted at two centres. Patients with HCV genotype 1 (n=25) and patients with HCV genotype 2 or 3 infection (n=10) without cirrhosis were treated with SOF+RBV for 12 weeks. Of the 10 patients with HCV genotype 2 or 3 infection, 4 (40%) had a genotype 2 infection and 6 (60%) had a genotype 3 infection. However, this regimen is not approved for HCV genotype 3 patients, but only for HCV genotype 2 patients (the minority of the population in this study arm).

The frequency of any AE was not reported in either study. The most common AEs were fatigue (16-48%), nausea (16-44%), headache (28-40%), dizziness (40%), anaemia (32%), insomnia (30%), and rash (30%). No one discontinued treatment due to AEs in one of the studies[202]; the other study didn't report this outcome[1]. Across all study groups, there were 3 serious AE: 1 urethral injury and 1 episode of furunculosis; the remaining one was not further specified. Grade 3/4 AEs occurred in 4-20% of patients in one study[202].The same study reported that there was no death[202] ; the other one didn't report these outcomes[1].

LDV+SOF with/without RBV

Afdhal[142] ION-1 study was a multi-centre, randomised, open-label trial conducted at 99 sites in the US and Europe. Patients with HCV genotype 1 infection with or without cirrhosis were randomly assigned into 4 groups receiving SOF+LDV with or without RBV for 12 weeks (with RBV n=217, without RBV n=214) or for 24 weeks (with/without RBV n=217 in each group), respectively.

Lawitz[10] LONESTAR study was a single-centre, open-label trial. Two cohorts of patients (treatment-naive in Cohort A and treatment-experienced in Cohort B) were randomly assigned to SOF+LDV with or without RBV for 8 or 12 weeks. In one group of Cohort A, 19 patients with HCV genotype 1 infection without cirrhosis received SOF+LDV for 12 weeks.

Kowdley[9] ION-3 study was a multi-centre, randomised, open-label trial conducted at 58 sites in the US. Patients with HCV genotype 1 infection without cirrhosis were randomised to three different treatment groups. In one group, 216 patients received SOF+LDV for 12 weeks.

In Gane[203] ELECTRON study both treatment-naive and treatment-experienced patients with HCV genotype 1 infection with or without cirrhosis were enrolled into different treatment groups. In one of these groups, 25 treatment-naive patients without cirrhosis received SOF+LDV+RBV for 12 weeks.

Across all studies, frequency of any AE ranged between 42% and 96%, although it was higher than 69% in all but one study[10]. The most frequent AEs were headache (15-44%), fatigue (21-38%), nausea (5-24%), insomnia (21-22%), diarrhea (11%), upper respiratory tract infection (5-36%), abdominal pain (5%), and back pain (5%). 0-4% of patients discontinued treatment due to an AE. Serious AEs occurred in <1-8% of patients, details of which can be seen in Appendix 1. Two studies reported on grade 3/4 AEs, which were seen in 3-12% of patients. No study reported on deaths as SAE.

DCV+SOF

Sulkowski[2] was a randomised, open-label trial. Previously untreated or treatment-experienced patients with HCV genotype 1, 2 or 3 without cirrhosis were randomly assigned to one of ten different treatment groups receiving DCV+SOF for varying durations with or without RBV. In group G, 41 treatment-naive patients with HCV genotype 1 infection received DCV+SOF for 12 weeks.

93% of patients reported any AE, the most common of which were fatigue (39%), headache (34%), and nausea (20%). There was one SAE (psoriasis); no patient discontinued treatment due to an AE. 1 patients experienced grade 3/4 AEs. There was no death during the study.

OBV+PAR+RIT with/without RBV

Hezode[204] PEARL-I study was a multi-centre, randomised, open-label trial conducted in Europe and the US. The study included both treatment-naive and treatment-experienced patients with HCV genotype 4 infection without cirrhosis. Treatment-naive patients were randomised to receive either OBV+PAR+RIT with RBV (n=42) or without RBV (n=44) for 12 weeks.

Among patients receiving the RBV-containing regimen, the frequency of any AEs was higher than among those receiving the RBV-free regimen (88% vs 77%). The most commonly reported AEs in both groups were headache (with RBV 33% vs without RBV 30%), asthenia (24% vs 25%), and nausea (17% vs 9%). There were no treatment discontinuations in either group. In the RBV-free regimen, one SAE occurred that was considered unrelated to the study medication; this was a contusion due to a traffic accident. Neither grade 3/4 AEs nor deaths were reported.

OBV+PTV+RIT+DSV with/without RBV

The Feld[149] SAPPHIRE-I study, was an international, multi-centre, randomised, double-blind trial conducted at 79 sites in North America, Europe, and Australia. Patients with genotype 1 HCV infection without cirrhosis were randomised to receive either OBV+PTV+RIT+DSV+RBV (n = 473) or placebo (n = 158) for 12 weeks.

Ferenci[150] PEARL III and PEARL IV studies were double-blind, placebo-controlled trials conducted at 53 sites internationally, including patients with HCV genotype 1 infection without cirrhosis. In the PEARL III study (patients with genotype 1b) and the PEARL IV study (patients with genotype 1a)[150], patients were randomised to receive OBV+PTV+RIT+DSV with RBV (100 genotype 1a; 210 genotype 1b) or without RBV (205 genotype 1a, 209 genotype 1b) for 12 weeks.

Across all three studies, the frequency of any AE ranged from 67% to 92%, the most common of which were fatigue (21-67%), headache (23-28%), nausea (4-21%), pruritus (4-17%), insomnia (3-17%), decreased Hb level (3-51%). In the SAPPHIRE-I study, the frequency of AEs were higher in patients receiving the active regimen compared with those receiving placebo (88% vs 73%, P<0.001). In both PEARL III and PEARL IV studies, AEs were more frequently reported in the RBV-containing regimens than in the RBV-free regimens (PEARL III 80% vs 67%, P=0.003; PEARL IV 92% vs 82%, P=0.03). Among other AEs, pruritus, nausea, and insomnia occurred at a higher frequency among patients who received RBV than among those who did not in one or both studies (P=0.02). Among the patients in PEARL IV who had a haemoglobin level within the normal range at baseline, 42% of patients who received the RBV-containing regimen and about 4% of patients who received the RBV-free regimen had a haemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). Similarly, in PEARL III, about 51% of patients who received RBV had a low haemoglobin level at the

end of treatment, as compared with around 3% of patients who did not receive RBV (P<0.001). Across all three studies, about 1-3% of patients discontinued treatment due to an AE. In 1 study 0-2% of patients experienced SAEs; in the other study SAEs were reported in detail but not in numbers/frequencies; details can be found in Appendix 1. None of the studies reported grade 3/4 AEs or death as SAE.

Treatment-experienced patients – AEs

In treatment-experienced patients (detailed characteristics for which can be found in Appendix 1), the following studies were identified:

- 1 study on SOF+RBV: Jacobson[155] FUSION study.
- 5 studies on SOF+LDV with or without RBV: Afdhal[142] ION-2, Lawitz[10] LONESTAR study, Cohort B, Bourliere[148] SIRIUS study, Gane[203] ELECTRON study, Group 12, Group 16 and Group 17, Osinusi[147] NIAID Synergy study.
- 1 study on DCV+SOF: Sulkowski[2], Group I.
- 1 study on OBV+PTV+RIT+RBV: Hezode[204] PEARL-I study.
- 2 studies on OBV+PTV+RIT+DSV with or without RBV: Zeuzem[145] SAPPHIRE-II study, and Andreone[152] PEARL-II study.

SOF+RBV

Jacobson[155] FUSION study was a multi-centre, randomised, placebo-controlled trial conducted at 67 sites in the US, Canada, and New Zealand. Treatment-experienced patients with HCV genotype 2 or 3 infection with or without cirrhosis received either SOF+RBV for 12 weeks followed by matching placebo for 4 weeks or 16 weeks of SOF+RBV. Since the regimen of SOF+RBV for 16 weeks is neither approved for genotype 2, nor for genotype 3 infection, we don't report this group here. Furthermore, the regimen of SOF+RBV for 12 weeks is only approved for genotype 2 but not for genotype 3 infection. However, the authors didn't report safety outcomes separately for the two genotypes. Of the 103 patients who received SOF+RBV for 12 weeks (and matching placebo for an additional 4 weeks), 3 (3%) had a genotype 1 infection, 36 (35%) had a genotype 2 infection, and the remaining 64 (62%) had a genotype 3 infection. Therefore, in the vast majority of patients SOF+RBV for 12 weeks was used off-label.

In Jacobson[155] FUSION study, the frequency of any AE was 89%, whereas it was not reported in Gane[1]. The most common AEs were fatigue (40-44%), insomnia (41%), headache (25-40%), and nausea (21%). While in the FUSION study 1% of patients discontinued treatment due to an AE, the ELECTRON study didn't report this outcome. Serious AEs occurred in 0-5% of patients; these were malignant hepatic neoplasm (3%); abdominal pain, esophageal varices haemorrhage, pyrexia, portal vein thrombosis, upper limb fracture, and basal cell carcinoma (1% each). Grade 3/4 AEs occurred in about 8% of patients (11% in patients with cirrhosis; 6% in patients without cirrhosis) in the FUSION study; there was no death. The ELECTRON study didn't report grade 3/4 AEs or deaths.

LDV+SOF

Afdhal[142] ION-2 was a multi-site, randomised, open-label study conducted at 64 sites in the US. Treatment-experienced patients with HCV genotype 1 infection with or without cirrhosis were randomised to four different groups receiving either SOF+LDV with (n=111) or without RBV (n=109) for 12 weeks or SOF+LDV with (n=111) or without RBV (n=109) for 24 weeks.

Lawitz[10] LONESTAR study was a single-centre, open-label trial. Two cohorts of patients (treatment-naive in Cohort A and treatment-experienced in Cohort B) were randomly assigned to SOF+LDV with or without RBV for 8 or 12 weeks. In Cohort B, patients with HCV genotype 1 infection with or without cirrhosis received SOF+LDV either with (n=21) or without RBV (n=19) for 12 weeks.

Bourliere[148] SIRIUS study was a multi-centre, randomised, double-blind, placebo-controlled trial conducted at 20 sites in France. Treatment-experienced patients with HCV genotype 1 infection with cirrhosis received SOF+LDV with or without RBV (n=77 in each group).

Osinusi[147] NIAID Synergy study was a single-centre, open-label, uncontrolled trial. 14 treatment-experienced patients with HCV genotype 1 infection with or without cirrhosis were treated with SOF+LDV for 12 weeks.

In Gane[203] ELECTRON study both treatment-naive and treatment-experienced patients with HCV genotype 1 infection with or without cirrhosis were enrolled into different treatment groups. In group 12, patients without cirrhosis received SOF+LDV+RBV for 12 weeks (n=9). In group 16 and 17, patients with cirrhosis received SOF+LDV without (n=10) or with RBV (n=9), respectively. Patients in all three groups were treatment-experienced.

Across all studies, any AE occurred in 37-100% of patients, however, in all but one study at least 50% of the patients had an AE. The most commonly reported AEs were fatigue (10-78%), headache (5-67%), nausea (6-44%), asthenia (45-58%), anaemia (29%), and pruritus (9-28%); other commonly reported AEs that were less frequent or reported in single trials can be seen in Appendix 1. Only in one of the trials that reported treatment discontinuations (all but the LONESTAR study), this outcome was reported for 1 patient. SAEs occurred in 0-10% of patients, details of which can be found in Appendix X. Grade 3/4 AEs were reported in two studies[147,203]and occurred in 0 to 4 patients (0-29%). Deaths were not reported in any study.

DCV+SOF

Sulkowski[2] was a randomised, open-label trial. Previously untreated or treatment-experienced patients with HCV genotype 1, 2, or 3 without cirrhosis were randomly assigned to one of ten different treatment groups receiving DCV+SOF for varying durations with or without RBV. In group I, 21 treatment-experienced patients with HCV genotype 1 infection received DCV+SOF for 24 weeks.

The frequency of any AE was 76%, the most common of which were headache (33%) and fatigue (29%). There were no treatment discontinuations, no SAEs, no grade 3/4 AEs and no deaths during the study.

OBV+PTV+RIT+RBV

Hezode[204] PEARL-I study was a multi-centre, randomised, open-label trial conducted in Europe and the US. The study included both treatment-naive and treatment-experienced patients with HCV genotype 4 infection without cirrhosis. Treatment-experienced patients (n=49) received OBV+PTV+RIT+RBV for 12 weeks.

88% of patients reported any AE, the most common of which were asthenia (33%), headache (29%), and fatigue (18%). There were no treatment discontinuations and no SAE. Grade 3/4 AEs and deaths were not reported.

OBV+PTV+RIT+DSV with/without RBV

Zeuzem[145] SAPPHIRE-II study was an international, multi-site, randomised, placebo-controlled, double-blind trial. Treatment-experienced patients with HCV genotype 1 infection without cirrhosis were randomised to OBV+PTV+RIT+DSV+RBV for 12 weeks (n=297) or matching placebos (n=97).

Andreone[152] PEARL-II study was a multi-centre, open-label trial that included treatment-experienced patients with HCV genotype 1 infection without cirrhosis. Patients received either OBV+PTV+RIT+DSV with RBV (n=91) or without RBV (n=95) for 12 weeks.

Across both studies, the frequency of any AE was 78-91%. The most commonly reported AEs were headache (23-36%), fatigue (16-33%), nausea (6-21%), pruritus (5-14%), and anaemia (0% without RBV vs 11% with RBV). In the SAPPHIRE-II study[145], the frequency of AEs was significantly greater in the active treatment group than in the placebo group (91% vs 83%, P=0.02), as was the frequency of pruritus (14% vs 5%, P=0.03). Fatigue was more frequent in the active treatment group than in the placebo group, without statistical significance (P=0.06). In the PEARL II study[152], there was no difference in the frequency of any AEs between patients receiving RBV and patients not receiving RBV

(79% vs 78%). While there was no difference in the frequency of headache between the two groups (24% vs 23%), both fatigue and nausea occurred more often in patients receiving RBV than patients not receiving RBV: fatigue (32% vs 16%; P=0.015); and nausea (21% vs 6%; P=0.005). In both studies, 1-2% of patients receiving RBV discontinued treatment due to an AE, while no patients in study arms without RBV discontinued treatment. SAEs occurred in about 2% of patients in active treatment groups across both studies and 1% of patients in the placebo group of one study[145]. In the SAPPHIRE-II study[145] these were chronic obstructive pulmonary disease, acute transient stroke (cerebrovascular accident), pneumonia, acute renal failure, and intestinal obstruction (in 1 patient each). Dizziness, nausea, vomiting, and bradycardia were reported in the same patient. Atrial fibrillation occurred in 1 patient in the placebo group. In the PEARL II study[152] SAEs included pancreatitis, cellulitis, nephrolithiasis, and osteoarthritis. Grade 3/4 AEs were reported in 1 patient in each of the studies; both patients received active treatment regimens. Deaths were not reported in either study.

Combined (treatment-naive and treatment-experienced) patients – AEs

In combined (treatment-naive and treatment-experienced) patients, the following studies were identified (detailed characteristics for which can be found in Appendix 1):

- 5 studies on SOF+RBV: Jacobson [155] POSITRON study, Omata[157], Zeuzem[158] VALENCE study, Ruane[161], and Foster[154]: BOSON study.
- 3 studies on SOF+LDV with or without RBV: Mizokami[143], Stedman[205] ELECTRON study, and Kohli[160];
- 3 studies on SMV+SOF with or without RBV: Modi[206], Pearlman[153] and Lawitz[151] COSMOS study.
- 1 study on DCV+SOF: Nelson[159] ALLY-3 study.
- 2 studies on OBV+PTV+RIT+DSV+RBV: Poordad[144] TURQUOISE-II study and Lalezari[182].

SOF+RBV

Jacobson[155] POSITRON study was a multi-centre, randomised, placebo-controlled trial conducted at 63 sites in the US, Canada, Australia and New Zealand. Patients with HCV genotype 2 or 3 infection with or without cirrhosis received either SOF+RBV for 12 (n=207) weeks or placebo (n=71).

Omata[157] was a multi-centre, open-label trial conducted at 20 sites in Japan that included patients with HCV genotype 2 infection with or without cirrhosis. 153 patients received SOF+RBV for 12 weeks.

Zeuzem[158] VALENCE study was a multi-centre, randomised trial, however, after a protocol amendment study group assignments were unblinded, the placebo group was terminated, patients with HCV genotype 2 infection were treated with SOF+RBV for 12 weeks and patients with HCV genotype 3 infection were treated with SOF+RBV for 24 weeks (unless they had already completed 12 weeks of treatment before the protocol amendment). In total, 85 patients with genotype 2 or 3 infection received placebo for 12 weeks, 84 patients with genotype 2 (n=73) or 3 (n=11) infection, respectively, received SOF+RBV for 12 weeks, and 250 patients with genotype 3 infection received SOF+RBV for 24 weeks.

Ruane[161] was a single-centre, randomised, open-label study conducted in the US. However, patients had to be born in Egypt to two parents of Egyptian ancestry. Patients with a HCV genotype 4 infection with or without cirrhosis were randomly assigned to SOF+RBV for 12 weeks (n=31) or 24 weeks (n=29).

Foster[154] BOSON study was a randomised, open-label study conducted at 80 sites in the UK, Australia, the US, Canada, and New Zealand. Patients with HCV genotype 2 infection with cirrhosis and patients with HCV genotype 3 infection with or without cirrhosis were included. They received either SOF+RBV for 16 weeks (n=196), or SOF+RBV for 24 weeks (n=199), or SOF+PR for 12 weeks (n=197). The latter regimen is described above.

The frequency of any AE across all studies ranged from 71% to 100%. The most frequent AEs were fatigue (19-52%), nausea (11-31%), headache (10-66%), nasopharyngitis (11-29%), pruritus (27%), asthenia (25%), anaemia (12%), and insomnia (24-52%). Between 0% and 10% of patients discontinued treatment due to an AE. SAE occurred in at least one study arm of all studies; the frequency across all arms varied from 0-10% (details can be found in Appendix 1). Grade 3/4 AE occurred in <1% to 10% of patients. Among the 2 studies that reported deaths (POSITRON and BOSON), no patient died during the study.

LDV+SOF with/without RBV

Mizokami[143] was a randomised, open-label study conducted at 19 clinical centres in Japan. Patients with HCV genotype 1 infection with or without cirrhosis were randomised to receive SOF+LDV with (n=170) or without RBV (n=171) for 12 weeks.

Stedman[205] reported a single arm of the ELECTRON trial. Patients with inherited bleeding disorders and HCV genotype 1 infection were treated at two centres in New Zealand. 14 treatment-naive or treatment-experienced patients, of whom one had a cirrhosis, received SOF+LDV+RBV for 12 weeks.

Kohli[160] was a single-centre, single-arm, open-label trial that enrolled patients with HCV genotype 4 infection with or without cirrhosis. 21 patients received SOF+LDV for 12 weeks.

Across all three studies, the frequency of AEs was 48-93%. The most common AEs were fatigue (14-50%), headache (7-36%), nasopharyngitis/upper respiratory tract infection (10-29%), headache (7-14%), nausea (10-29%), anaemia (14% in the RBV arm of Mizokami[143], fatigue (14%), diarrhea (10% each), and malaise (5%). In Mizokami[143], 2 patients (1%) in the group receiving RBV discontinued treatment due to an AE; in Stedman[205] and Kohli[160] no patient discontinued treatment due to an AE but in Kohli[160] one patient was non-adherent to the study drugs and discontinued the study at week 5. Among the two study arms of Mizokami[143], 1-2% of patients experienced SAEs, including hepatocellular carcinoma, oesophageal varices, haemorrhage, wrist fracture, acute myocardial infarction, and cardia arrest. Grade 3/4 AE were not reported. In the RBV-containing study arm, 1 patient died during the study. In Stedman[205], there were two SAEs (syncope and cholelithiasis in one patient each) that were unrelated to treatment. Neither grade 3/4 AEs nor deaths were reported. Kohli[160] reported that there were no SAEs, no grade 3/4 AEs, and no deaths during the study.

SMV+SOF with/without RBV

Modi[206] was an open-label cohort study; data was gathered prospectively from a treatment cohort of decompensated monoinfected genotype 1 chronic HCV patients with cirrhosis treated at two large hepatology referral centres in the US. In total, 42 patients were treated with SMV+SOF with (n=7) or without RBV (n=35), respectively, of whom 19 (45%) were listed for liver transplantation.

Pearlman[153] was a randomised, open-label trial that enrolled patients with HCV genotype 1 infection with cirrhosis. Patients received either SMV+SOF for 12 weeks (n=62; 58 in final analysis) or SOF+PR for 12 weeks (n=31; 24 in final analysis). The latter group is not described here.

Lawitz[151] COSMOS study was a multi-centre, randomised, open-label trial conducted in 23 centres in the US. Patients with HCV genotype 1 infection with or without cirrhosis received SMV+SOF for 12 weeks with (n=54) or without (n=28) RBV.

Across all three studies, the frequency of any AE was 43-85%. The most frequent AEs were rash (11-20%), fatigue (14%), pruritus (9-14%), anaemia (10-13%), headache (12%), nausea (10%), insomnia (10%), and photosensitivity conditions (7%). No patient in any study discontinued treatment due to an AE. Furthermore, none of the studies reported a SAE. Grade 3/4 AEs occurred in 7% (without RBV) and 11% (with RBV) of patients, respectively, in the COSMOS study. There was no death in any of the studies.

DCV+SOF

Nelson[159] ALLY-3 study was an open-label, two-cohort study including patients with HCV genotype 3 infection with or without cirrhosis. The two cohorts of treatment-naive (n=101) and treatment-experienced (n=51) patients received DCV+SOF for 12 weeks. The authors reported safety outcomes combined for the overall group of 152 participants. The frequency of any AE was not reported,

however the most common AEs were headache (20%), fatigue (19%), and nausea (12%). There was no discontinuation of treatment due to an AE. There was one SAE (gastrointestinal haemorrhage) that was considered unrelated to study medication. The authors reported grade 3/4 AEs in 2% of patients. No patient died during the study.

OBV+PTV+RIT+DSV+RBV

Poordad[144] TURQUOISE-II study was an international, multi-site, randomised, open-label trial conducted at 78 sites in North America and Europe. Patients with HCV genotype 1 infection with cirrhosis received either OBV+PTV+RIT+DSV+RBV for 12 weeks (n=208) or for 24 weeks (n=172).

In total, more than 90% of patients in each study arm reported any AE, the most common of which were fatigue (33% in the 12-week group vs 47% in the 24-week group, P<0.01), headache (28% and 31%, respectively), nausea (18% vs 20%), anaemia (8% vs 11%), and dyspnea (6 vs 12%, P<0.05). In each group, 2% of patients discontinued treatment due to AEs. SAEs occurred in 5% and 6% of patients in the 12-week group and the 24-week group, respectively; details can be found in Appendix 1. The most frequent grade 3 or 4 laboratory abnormalities observed during the treatment period were elevations in total bilirubin levels (in 37 of 380 patients [9.7%]), which predominantly reflected elevated indirect bilirubin values. 1 patient in the 12-week group had severe lactic acidosis in the context of metformin use and a subsequent ischemic liver injury requiring liver transplantation. He died from complications after liver transplantation, including multiorgan failure and septic shock that began 80 days after the last dose of the study drug.

Lalezari[182] was a phase II, multicentre, open-label, single-arm study in treatment naive or treatment experienced HCV genotype 1-infected patients without cirrhosis (on methadone or buprenorphine±naloxone). Patients (n=38) received OBV+PTV+RIT+DSV+RBV for 12 weeks. The majority (92.1%) experienced at least one AE. The most common AEs were nausea (50%), fatigue (47.4%), headache (31.6%), insomnia (18.4%), rash (15.8%); two (5.3%) experienced SAEs.

The table 6.3. provdes a summary of different categories of AEs.

Table 6.3. Any AEs, the most frequent AEs, SAEs, discontinued treatment due AEs with six DAAs under assessment, in regimens without IFN [2,9,10,142-155,157-161,202-204,206]

Drug combination and studies	Any AEs N (%)	The most frequent AEs (%)	SAEs N (%)	Discontinued treatment due AEs n (%)
SOF				
Jacobson et al. (2013) [155] POSITRON study: SOF12+RBV12	185 (89.4)	fatigue (44), nausea (22), headache (21)	11 (5.3)	5 (2.4)
Osinusi et al. (2013)[202]: SOF24 + RBV24; SOF24 + RBV24 (600mg)	NR	anaemia (32), headache (28), fatigue (16), nausea (16); headache (28), fatigue (24), nausea (20)	0; 1 (4)	0; 0
Ruane et al. (2015)[161] SOF12 + RBV12; SOF24 + RBV24	28 (90); 29 (100)	headache (58), insomnia (52), fatigue (45); headache (66), insomnia (48), fatigue (52)	0; 3 (10)	0; 0
Jacobson et al. (2013)[155] FUSION study: SOF12+RBV12	92 (89.3)	headache (25), fatigue (45), nausea (21)	5 (4.9)	1 (1)
Zeuzem et al. (2014)[158] VALENCE	72 (86);	nausea (31), headache	0;	1 (1);

study: SOF12+RBV12; SOF24+RBV24	229 (92)	(29), asthenia (25); fatigue (30), headache (30) pruritus (27)	10 (4)	1 (<1)
Foster et al. (2015)[154] BOSON study: SOF16+RBV16; SOF24+RBV24	185 (94); 188 (95)	fatigue (36), headache (31), insomnia (24); fatigue (41), headache (36), insomnia (28)	8 (4); 10 (5)	3 (2); 3 (2)
Omata et al. (2014)[157] SOF12+RBV12	112 (73)	nasopharyngitis (29), anemia (12), headache (10)	2 (1)	0
LDV+SOF				
Lawitz et al. (2014)[10] LONESTAR study: Cohort A: SOF12+LDV12 Cohort B: SOF12+LDV12; SOF12+LDV12+RBV12	8 (42) 7 (37); 12 (57)	(5) each: nausea, upper respiratory tract infection, abdominal pain, back pain nausea (19), upper respiratory tract infection (19), each (5): bronchitis, headache, back pain, decrease appetite	1 (5); 1 (5); 1 (5)	NR; NR; NR;
Kowdley et al. (2014)[9] ION-3 study: SOF12+LDV12	149 (69)	fatigue (23), headache (15), nausea (11)	5 (2)	2 (1)
Osinusi et al. (2014)[147] NIAID study: SOF12+LDV12	7 (50)	myalgia (14), each (7): loose stool, constipation, headache, nasal congestion, pruritic rash	0	0
Bourliere et al. (2015)[148] SIRIUS study: SOF12+LDV12+RBV12 ; SOF24+LDV24	75 (96); 67 (87)	asthenia (58), headache (27), pruritus (28); asthenia (45), headache (40), pruritus (9);	4 (5); 8 (10)	1 (1); 0
Gane et al. (2014)[203] ELECTRON study: SOF12+LDV12+RBV12 ; SOF12+LDV12+RBV12 ; SOF12+LDV12+RBV12 ; SOF12+LDV12	24 (96); 9 (100); 8 (89); 7 (70)	headache (44), insomnia, fatigue (24), nausea (24), upper respiratory tract infection (36), gastroenteritis; fatigue (78), headache (67), insomnia (44); nausea (44), each (22) headache, vomiting, arthralgia, anxiety, conjunctivitis, gastroesophageal reflux; headache (30); gastroenteritis (22); (10) each: fatigue; upper respiratory tract infection; cough	NR; NR; NR; NR	1 (4); 0; 0; 0

Mizokami et al. (2015)[143]: SOF12+LDV12; SOF12+LDV12+RBV12	112 (65); 128 (75)	nasopharyngitis (29), headache (7), malaise (5); nasopharyngitis (24), anaemia (14), headache (9)	3 (2); 2 (1)	0; 2 (1)
Afdhal et al. (2014)[142] ION-1 study: SOF12+LDV12; SOF24+LDV24; SOF12+LDV12+RBV12; SOF24+LDV24+RBV24	168 (79); 185 (85); 178 (82); 200 (92)	headache (25), fatigue (21), nausea (11), diarrhea (11) ; fatigue (36), headache (23), insomnia (21); fatigue (24), headache (25), nausea (13); fatigue (38), headache (30), insomnia (22)	1 (<1); 7 (3); 18 (8); 7 (3)	0; 0; 4 (2); 6 (3)
Afdhal et al. (2014)[146] ION-2 study: SOF12+LDV12; SOF24+LDV24; SOF12+LDV12+RBV12; SOF24+LDV24+RBV24	73 (67); 88 (81); 96 (86); 100 (90)	fatigue (21), headache (26), nausea (12); fatigue (24), headache (23), nausea (6); fatigue (41), headache (23), nausea (18); fatigue (45), headache (32), nausea (23)	0; 6 (6); 0; 3 (3)	0; 0; 0; 0
Stedman et al. (2015)[205]: LDV12+SOF12+RBV12	13 (93)	fatigue (50), headache (36), nausea (29)	2	0
Kohli et al. (2015)[160]: LDV12+SOF12	10 (48)	diarrhoea (10), fatigue (14), nausea (10), upper respiratory tract infection (10)	0	0
SMV				
Pearlman et al. (2015)[153]: SMV12+SOF12	46 (79)	rash (17) , fatigue (14), headache (12)	NR	0
Lawitz et al. (2014) [151] COSMOS study: SMV12+SOF12+RBV12; SMV12+SOF12	46 (85); 20 (71)	rash (20), anemia (13), pruritus (9); pruritus (14), rash (11), photosensitivity conditions (7)	0	0
Modi et al. (2015)[206]: SMV12+SOF12; SMV12+SOF12+RBV12	18 (43)	fatigue (14), headache (12), nausea (10), insomnia (10), anaemia (10)	0	0
DCV				
Nelson et al. (2015)[159] ALLY-3 study: DCV12+SOF12	NR	headache (20), fatigue (19), nausea (12)	1 (1)	0
Sulkowski et al. (2014)[2]	38 (93);	fatigue (39), headache (34), nausea (20);	1 (2); 0	0; 0

DCV12+SOF12; DCV24+SOF24	17 (76)	headache (33), fatigue (29), nausea 0		
OBV+PTV+RIT				
Hezode et al. (2015)[204] PEARL-I study: OMB12+PAR12+RIT12 ; OMB12+PAR12+RIT12 +RBV12	34 (77); 37 (88)	headache (30); asthenia (25); nausea (9); headache (33); asthenia (24); nausea (17)	1 (2); 0	0
OBV+PTV+RIT+DSV				
Feld et al. (2014)[149] SAPPHIRE-I study: OMB12+PAR12+RIT12 +DAS12+RBV12	414 (87.5)	fatigue (34.7), headache (33), nausea (16.9), pruritus (16.9)	10 (2.1)	3 (0.6)
Poordad et al. (2014)[144] TURQUOISE-II study: OMB12+PAR12+RIT12 +DAS12+RBV12; OMB24+PAR24+RIT24 +DAS24+RBV24	191 (92); 156 (91)	fatigue (33), headache (28), pruritus (18), nausea (18), anaemia (8), dyspnea (6); **fatigue** (47, statistically significant difference) , headache (31), pruritus (19), nausea (20), anaemia (11), **dyspnea** (12, statistically significant difference)	13 (6); 8 (5)	4 (2); 4 (2)
Ferenci et al. (2014)[150] PEARL III, PEARL IV studies: OMB12+PAR12+RIT12 +DAS12; OMB12+PAR12+RIT12 +DAS12+RBV12	169 (82); 92 (92)	fatigue (35.1), headache (28.3), nausea (13.7), insomnia (7.8), pruritus (5.9), decreased haemoglobin (3.9); fatigue (46), headache (25), nausea (21), **insomnia** (17, statistically significant difference) , pruritus (10), **decreased haemoglobin** (42, statistically significant difference)	4 (1.9); 4 (1.9)	1 (0.5); 3 (3)
Zeuzem et al. (2014)[145] SAPPHIRE-II study: OMB12+PAR12+RIT12 +DAS12+RBV12	271 (91.2)	headache (36.4), fatigue (33.3), nausea (20.2), pruritus (13.8)	6 (2.0)	3 (1.0)
Andreone et al. (2014)[152] PEARL II study: OMB12+PAR12+RIT12 +DAS12+RBV12; OMB12+PAR12+RIT12 +DAS12	72 (79.1); 74 (77.9)	**fatigue** (32, statistically significant difference), headache (24), **nausea** (21, statistically significant difference**), insomnia** (14), pruritus (14), **anaemia** (11, statistically significant difference) ; headache (23), fatigue (15.8), nausea (6.3); pruritus (8.4); anaemia (0)	2 (2.2); 2 (2.1)	2 (2.2); 0

Lalezari et al. (2015)[182] OMB12+PAR12+RIT12 +DAS12+RBV12	35 (92.1)	nausea (50), fatigue (47.4), headache (31.6), insomnia (18.4), rash (15.8)	2 (5.3)	1 (2.6)

12 = 12 weeks; 16 = 16 weeks; 24 = 24 weeks; 48 = 48 weeks; AE = adverse event; DAA = direct-acting antiviral; DAS = dasabuvir; DCV = daclatasvir; IFN = interferon; LDV = ledipasvir; OMB = ombitasvir; PAR = paritaprevir; PR = pegylated interferon and ribavirin; QD = once daily; RBV = ribavirin; RGT = response-guided therapy; RIT = ritonavir; SAE= serious adverse event ; SMV = simeprevir; SOF = sofosbuvir

In conclusion, with six DAAs under assessment, in regimens without IFN, the frequency of any AEs reported was within the range of 40%-100%. SAEs were reported with a frequency of 1%-10%. The most common AEs reported in treatment-naive patients for the new oral drugs under assessment were headache, fatigue, insomnia, and nausea.

In one study[150], on OBV12+PTV12+RIT12+DSV12, with or without RBV, AEs of pruritus, nausea, and insomnia occurred at a statistically higher frequency among patients who received RBV than among those who did not (P=0.02). This was also the case for low haemoglobin levels.
As in treatment-naive patients, the most common AEs reported in treatment-experienced patients for the new oral DAAs drugs under assessment were headache, fatigue, insomnia, and nausea.

In one study[152] on OBV12+PTV12+RIT12+DSV12, with or without RBV, fatigue, nausea, insomnia, anemia, rash, increased blood bilirubin levels, and low haemoglobin levels occurred at a statistically higher frequency among patients who received RBV than among those who did not (P<0.001-0.017).

In combined patient groups, as reported in treatment-naive patients and treatment-experienced patients, the most common AEs reported for the new oral drugs under assessment were headache, fatigue, insomnia, and nausea.

In one study[144] on OBV12+PTV12+RIT12+DSV12+RBV12 or RBV24, fatigue and dyspnoea were statistically significantly higher in the RBV24 group.

[C0002] Are the harms related to dosage or frequency or administration of the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in relation to the comparators and to each other?

[C0004] How does the frequency or severity of harms change over time or in different settings of the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in relation to the comparators and to each other?

Overall, 13 studies (in 11 publications) were identified with different dosing regimens or durations of treatment on sofosbuvir, ledipasvir plus sofosbuvir, simeprevir, and ombitasvir plus paritaprevir plus ritonavir plus dasabuvir to answer these questions.

Interferon-containing regimens for genotype 1 HCV infection

Five studies (in 4 publications[7,8,11,12]) were identified on interferon-containing regimens for genotype 1 HCV infection and included in this assessment despite the fact that dose of simeprevir was lower than approved and written in the SmPC.

SMV + PR

Treatment-naive patients

Two studies[7,12] were identified, in which low doses of SMV (50 to 100 mg instead of 150 mg according to the SmPC of simeprevir) were administered; both were conducted in treatment-naive Japanese patients.

CONCERTO-1[12] was a phase III, randomised, double-blind, placebo-controlled trial in which treatment-naive adults (≤ 70 years) with genotype 1 chronic HCV infection were randomised to receive

either SMV 100 mg once daily (QD for 12 weeks + PR response-guided therapy (RGT) for 24 or 48 weeks), or placebo for 12 weeks + PR for 48 weeks.

SMV was well tolerated; the rates of discontinuations due to AEs were similar for the SMV+PR group and the PR alone group. The most frequent AEs in both groups were neutropenia (79% vs 82% for the SMV+PR group vs PR alone group, respectively), anaemia (79% vs 75%), and rash (56% vs 70%). SAEs were reported more frequently in the PR alone group then in the SMV+PR group (10% vs 3.3%). There were no deaths in either group.

The DRAGON study[7], was a multicentre, randomised clinical trial performed in Japan, in which 92 patients received SMV 50 or 100 mg QD for 12 or 24 weeks + PR for 24 or 48 weeks, according to RGT criteria (SMV12+PR24/48 or SMV24+PR24/48 for 50 mg and 100 mg), or PR for 48 weeks (PR48).

SMV was well tolerated; the incidence of AEs or discontinuations due to AEs between groups was similar in patients receiving SMV+PR and those receiving PR alone. The most frequent AEs were white blood cell count decrease (60-90% vs 77% for the SMV+PR groups vs PR alone group, respectively), neutrophil count decrease (77-92% vs 70%), rash (58%-78% vs 62%), malaise (62-63% vs 62%), and headache (62% vs 62%). SAEs were reported more frequently in the SMV+PR groups than in the PR alone group (8-12% vs 0%). One death was reported in the SMV12+PR24 100 mg group 3 weeks after the end of treatment (64-year-old female with hypertension in medical history developed cerebral infarction) and was considered unrelated to study drug treatment.

In conclusion, AEs were reported with a high frequency (more than 60% of patients) across both studies; the most frequent were neutropenia, anaemia and rash. Overall, the AE profile in patients treated with SMV+PR was comparable to that in patients who received PR alone, in both studies.

Treatment-experienced patients

Two studies (reported in one publication[8]) were found, in which a low dose of SMV (100 mg instead of 150 mg according to the SmPC of simeprevir) was administered to treatment-experienced Japanese patients.

CONCERTO-2 and CONCERTO-3[8] were phase III, open-label trials that investigated the efficacy and safety of SMV+PR. In CONCERTO-2, prior non-responders to interferon (IFN)-based therapy (N = 106) received SMV 100 mg QD for 12 weeks (n = 53) or 24 weeks (n = 53) in combination with PR RGT for 24 or 48 weeks. In CONCERTO-3, relapsers after IFN-based therapy (N = 49) received SMV 100 mg QD for 12 weeks in combination with PR RGT for 24 or 48 weeks. AEs were reported across the 2 studies in 70-100% of patients receiving SMV+PR; the most frequent were pyrexia, white blood cell count decrease, neutrophil count decrease, and anaemia (each previously mentioned AE in approximately 60% of patients in each study) (Table 6.4). Discontinuations due to AEs, and SAEs were infrequent. In the CONCERTO-2 study, 6 SAEs were reported in 5 patients: erythema multiforme; hypoesthesia; anaemia; laceration; acute pyelonephritis and ureteric calculus. In the CONCERTO-3 study, 7 SAEs were reported in 6 patients: malaise and nausea; pneumonia; cerebral haemorrhage; appendicitis; herpes zoster; and female breast cancer. No deaths were reported in either study[8].

In conclusion, the overall AE profile in treatment-experienced patients treated with SMV+PR was comparable to that in treatment-naive patients treated with SMV+PR.

Combined (treatment-naive and treatment-experienced) patients

In combined treatment-naive and treatment-experienced patients, 1 study of SMV+PR was found (CONCERTO-4)[11] in which a low dose of SMV (100 mg instead of 150 mg according to the SmPC of simeprevir) was administered to patients in Japan. CONCERTO-4[11] was an open-label, non-comparative, multicentre study of SMV 100 mg QD for 12 weeks + PR for 24 or 48 weeks in 79 patients; the most frequent AEs were pyrexia (85%), white blood cell count decrease (58%), and anaemia (50%). Three patients (4%) discontinued study drugs due to AEs, and 2 SAEs were reported (peripheral T-cell lymphoma and hyperbilirubinaemia). Grade 3/4 AEs occurred in 23% of patients. There was no death reported.

In conclusion, the overall AE profile in combined treatment-naive and treatment-experienced patients treated with SMV+PR was comparable to that in treatment-naive and treatment-experienced patients treated with SMV+PR.

Table 6.4. The most frequently reported AEs with SMV+PR in genotype 1 patients, according the different dosage (50 mg or 100 mg) or different time period of treatment

Drug combination and studies	The most frequent AEs
SMV+PR	
Hayashi et al. (2014) CONCERTO-1 study[12] SMV **100 mg**[a] 12 + PR12 followed by PR12-36 RGT; PR12 followed by PR36 RGT	neutropenia, anaemia, rash
Hayashi et al. (2014) DRAGON study[7] SMV **50 mg**[a] 12 + PR24/48; SMV **50 mg**[a] 24 + PR24/48; SMV **100 mg**[a] 12 + PR24/48; SMV **100 mg**[a] 24 + PR24/48; PR48	white blood cell count decreased, malaise, neutrophil count decreased
Izumi et al. (2014) CONCERTO-2 and 3 studies[8] **CONCERTO-2** (prior non-responders to IFN-based therapy): SMV **100 mg**[a] 12 + PR12 followed by PR12-36 RGT; SMV **100 mg**[a] 24 + PR24 followed by PR0-24 RGT; **CONCERTO-3** (relapsers after IFN-based therapy): SMV **100 mg**[a] 12 + PR12 followed by PR12-36 RGT	pyrexia, white blood cell decreased, anaemia
Kumada et al. (2015) CONCERTO-4 study[11] SMV **100 mg**[a] 12 + PR12 followed by PR24/48 RGT	pyrexia, white blood cell decrease, anaemia

12 = 12 weeks; 24 = 24 weeks; 48 = 48 weeks; AE = adverse event; IFN = interferon; PR = pegylated interferon and ribavirin; QD = once daily; SMV = simeprevir; RGT = response- guided therapy

[a] Summary of Product Characteristics for SMV = 150 mg.

Interferon-free regimens for HCV infection (Table 6.3.)

Eight studies reported on interferon-free regimens, in different doses and different treatment period (three on SOF[154,158,161]; three on LDV+SOF[142,146,161]; one on DCV[2], and one on OBV+PTV+RIT+DSV+RBV[144]). Studies are described in assessment elements C0008 a and C0008 b and Table 6.3.).

SOF

In the three studies[154,158,161] described below, it can be seen that different doses of SOF and different periods of SOF administration (12 - 24 weeks) did not cause different safety outcomes. In one study[161], the most frequent AEs in both treatment groups were headache (58% vs 66%), insomnia (52% vs 48%), and fatigue (45% vs 52%), for SOF12 + weight-based RBV12 vs SOF24 400 mg + weight-based RBV24, respectively.

In the VALENCE study[158], the most frequent AEs in both treatment groups were headache (29% vs 30%) for SOF12+RBV12 vs SOF24+RBV24, respectively.

In the BOSON study[154], the most frequent AEs in both treatment groups were fatigue (36% vs 41%), headache (31% vs 36%), and insomnia (24 vs 28%) for SOF16+RBV16 vs SOF24+RBV24, respectively.

LDV+SOF

In the three studies[142,146,161] described below, it can be seen that different doses of LDV+SOF and different periods of LDV+SOF administration (12 - 24 weeks) did not cause different safety outcomes.

In the SIRIUS study[148], the most frequent AEs in both treatment groups were asthenia (58% vs 45%), headache (27% vs 40%), and pruritus (28% vs 9%) for SOF12+LDV12+RBV12 vs SOF24+LDV24, respectively.

In the ION-1 study[142], the most frequent AEs in treatment groups were headache (23%-30%), fatigue (21%- 38%), and nausea (11% - 13%) for SOF12+LDV12 and SOF24+LDV24, respectively. Among patients who received LDV–SOF without RBV, the incidence of AEs was similar in the 24-week group and in the 12-week group (85% vs 79%).

In the ION-2 study[146], the most frequent AEs were fatigue (21% vs 24%), headache (26% vs 23%), and nausea (12% vs 6%), for SOF12+LDV12 and SOF24+LDV24, respectively. Among patients who received LDV–SOF without RBV, the incidence of AEs was higher in the 24-week group than in the 12-week group (81% vs 67%).

DCV

In the Sulkowski study[2] the frequency of AEs was similar in 12 (93%) and 24 (76%) weeks treatment groups; in both groups the most common AEs were fatigue and headache, but nausea was frequent in 12 weeks treatment group.

OBV+PTV+RIT+DSV+RBV

In the TURQUOISE-II study[144], the most common AEs in the OBV12+PTV12+RIT12+DSV12+RBV12 and OBV24+PTV24+RIT24+DSV24+RBV24 groups were fatigue, headache, pruritus, nausea, anaemia, and dyspnoea. Fatigue and dyspnoea were reported by a statistically significant higher percentage of patients in the group treated for 24 weeks.

In conclusion, harms are not related to the dosage or frequency of administration for the majority of studies listed above. The frequency of harms did not change over the observed time period of 12 or 24 weeks, for the majority of combinations. A statistically significant difference was found for the combination of OBV+PTV+RIT+DSV+RBV in the TURQUOISE-II study[144]. Fatigue and dyspnoea were statistically significantly higher in the group of patients treated for 24 weeks. Also, in the ION-2 study[146] (SOF12+LDV12 and SOF24+LDV24), among patients who received LDV–SOF alone, the incidence of AEs was higher in the 24-week group than in the 12-week group (81% vs 67%).

[C0005] What are the susceptible patient groups that are more likely to be harmed with the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) in relation to the comparators and to each other?

Eleven studies, found on HIV-coinfected and pre- or post-liver transplanted patients, are described below. Summary data are listed in Table 6.5. and table 6.6.

HIV coinfection, treatment-naive or treatment-experienced or combined (treatment-naive or treatment-experienced)

The following studies were identified in HIV-coinfected patients (Table 6.5; detailed characteristics for which can be found in Appendix 1, section 1.2):

- 1 study on SOF+RBV: Molina[169] PHOTON-2 study.
- 2 studies on SOF+LDV: Osinusi[171] and Naggie[170] ION-4 study.
- 1 study on DCV+SOF: Wyles[175] ALLY-2 study.
- 1 study on OBV+PTV+RIT+DSV+RBV: Sulkowski[174] TURQUOISE-I study

SOF+RBV

Molina[169] PHOTON-2 study was a multi-centre, non-randomised, uncontrolled, open-label trial conducted at 45 clinical sites in Australia and Europe. Treatment-naive patients with HCV genotype 1, 3, or 4 infection with or without cirrhosis received SOF+RBV for 24 weeks (n=200); those with HCV genotype 2 infection with or without cirrhosis received SOF+RBV for 12 weeks (n=19). Treatment-experienced patients with HCV genotype 2 or 3 infection with or without cirrhosis received SOF+RBV for 24 weeks (n=55). All patients were co-infected with HIV.

The frequency of AEs ranged from 85% to 91% across all treatment groups. The most common AEs were fatigue (20-26%), asthenia (20%), insomnia (16-18%), headache (13-18%), and nausea (16%). 2-3% of patients in the two 24-week-groups discontinued treatment due to an AE. SAEs only occurred in the two 24-week-groups, in 5-9% of patients; details can be found in Appendix 1. Grade 3/4 AEs and deaths were not reported.

LDV+SOF

Osinusi[171] was single-centre, non-randomised, uncontrolled study. Treatment-naive patients with HCV genotype 1/HIV-coinfection without cirrhosis received SOF+LDV for 12 weeks (n=50).

Naggie[170] ION-4 study was a multi-centre, single-group, open-label study conducted at 60 sites in the US, Puerto Rico, Canada, and New Zealand. Both treatment-naive and treatment-experienced patients co-infected with HCV genotype 1 or 4 and HIV with or without cirrhosis received SOF+LDV for 12 weeks (n=335). The vast majority had a HCV genotype 1 infection (98%).

Across both studies, the frequency of any AE was 77-100%. The most common AEs were headache (10-25%), fatigue (10-21%), nasal congestion (16%), myalgia (14%), and diarrhea (11%). There were no treatment discontinuations due to AEs in either study. 2% of patients experienced SAEs in either study, the most common were pneumonia, hepatocellular carcinoma, and portal vein thrombosis (which can be found in Appendix 1). Grade 3/4 AEs were not reported in either study. In ION-4 study, one patient died, while in the study by Osinusi[171] there was no death.

DCV+SOF

Wyles[175] ALLY-2 study was an multi-centre, open-label study conducted in the US involving 203 treatment-naive and treatment-experienced patients coinfected with HCV genotype 1 to 4 and HIV with or without cirrhosis. The enrolment of patients with HCV genotypes other than 1 was limited to 20%. Overall, 83% of patients were infected with HCV genotype 1, and the remaining 17% were infected with HCV genotype 2 (9%), 3 (6%), or 4 (2%). Patients were treated in three groups: 101 treatment-naive patients and 52 treatment-experienced patients received DCV+SOF for 12 weeks; the remaining 50 treatment-naive patients received DCV+SOF for 8 weeks; since this is not an approved regimen, this group is not reported here.

Across the two treatment-groups, 71-73% of patients experienced any AE, the most common of which were fatigue (19% in both arms), nausea (14 vs 15%), and headache (12 vs 15%). There were no treatment discontinuations due to an AE. 1% and 6% of patients previously untreated and treated, respectively, experienced a SAE, including priapism, presyncope plus chest pain, drug abuse plus pulmonary embolism, and syncope plus hypertensive crisis; none was deemed to be related to a study drug by investigators. 2% vs 8% of patients experienced grade 3/4 AEs. In the treatment-naive group, 1 patient died due to cardiomyopathy and multiorgan failure at post-treatment week 24.

OBV+PTV+RIT+DSV+RBV

Sulkowski[174] TURQUOISE-I study was multi-centre, randomized, open-label study involving 63 treatment-naive and treatment-experienced patients with HCV genotype 1 and HIV-1 co-infection. Patients with cirrhosis were included also. Patients were randomized to receive OBV+PTV+RIT+DSV+RBV for 12 or 24 weeks.

Any AEs occurred in 56 of 63 patients (89%); no SAEs were reported and no patients discontinued HCV therapy because of AEs. The most common AEs were fatigue in 30 (48%), insomnia in 12 (19%), nausea in 11 (17%), and headache in 10 (16%) patients.

In conclusion, AEs were common with HIV coinfection, ranging from 70% to 100%. The most common AEs were fatigue, insomnia, and headache for studies on SOF+RBV and SOF+LDV.

For the study on DCV12+SOF12, the most frequent AEs were fatigue, nausea, and headache; for studies on OBV+PTV+RIT+DSV+RBV the most common AEs were fatigue, insomnia, nausea, and headache.

The table below summarises any AEs, the most frequent AEs, SAEs, discontinued treatment due AEs with six DAAs under assessment, in regimens without IFN, with HIV coinfection.

Table 6.5. Any AEs, the most frequent AEs, SAEs, discontinued treatment due AEs with six DAAs under assessment, in regimens without IFN, with HIV coinfection [169-171,174,175]

Drug combination and studies	Any AEs N (%)	The most frequent AEs (%)	SAEs N (%)	Discontinued treatment due AEs n (%)
SOF				
Molina et al. (2015)[169] PHOTON-2 study: SOF12+RBV12; SOF24+RBV24; SOF24+RBV24;	17 (89); 182 (91); 47 (85)	fatigue (26), insomnia (16), nausea (16); fatigue (20), insomnia (18), headache (18); fatigue (20); asthenia (20); headache (13)	0; 10 (5); 5 (9)	0; 5 (3); 1 (2)
LDV+SOF				
Osinusi et al. (2015)[171]: SOF12+LDV12	50 (100)	nasal congestion (16), myalgia (14), headache (10), fatigue (10)	1 (2)	0
Naggie et al. (2015)[170] ION-4 study: SOF12+LDV12	257 (77)	headache (25), fatigue (21), diarrhea (11)	8 (2)	0
DCV				
Wyles et al. (2015)[175] ALLY-2 study: DCV12+SOF12; DCV12+SOF12	74 (73); 37 (71)	fatigue (19), nausea (14), headache (12); fatigue (19), nausea (15), headache (15)	1 (1); 3 (6)	0; 0
OBV+PTV+RIT+DSV+RBV				
Sulkowski et al. (2015)[175] TURQUOISE-I study: OMB12+PAR12+RIT 12+DAS12+RBV12; OMB24+PAR24+RIT 24+DAS24+RBV24	56 (89)	fatigue (48),insomnia (19), nausea (17), headache (16);	0	0

12 = 12 weeks; 24 = 24 weeks; 48 = 48 weeks; AE = adverse event; DAA = direct-acting antiviral; DAS = dasabuvir; DCV = daclatasvir; IFN = interferon; LDV = ledipasvir; OMB = ombitasvir; PAR = paritaprevir; RBV = ribavirin; RIT = ritonavir ; SAE= serious adverse event ; SOF = sofosbuvir

Pre- or post-liver transplantation /treatment-naive, or treatment-experienced, or combined (treatment-naive or treatment-experienced)/

Overall, six single arm studies were identified in pre- or post-liver transplant patients (Table 6.6.; detailed characteristics for which can be found in Appendix 1):

- 2 studies on SOF+RBV: Curry[181] and Charlton[180].
- 1 study on SOF+LDV+RBV: Charlton[176] SOLAR 1.
- 2 studies on SMV+SOF with or without RBV: Punzalan[178] and Pungpapong[179].
- 1 study on OBV+PTV+RIT+DSV+RBV: Kwo[177] CORAL-I.

SOF+RBV

Curry[181] was an open-label study conducted at 13 centres in the US, 1 in New Zealand, and 1 in Spain. Treatment-experienced patients with HCV infection of any genotype with cirrhosis who were on the waiting list for liver transplantation were treated with SOF+RBV for 48 weeks (n=61).

89% of patients reported any AE, the most common being fatigue (38%), headache (23%), and anaemia (21%). 3% of patients discontinued treatment due to an AE. 18% of patients experienced SAEs (details can be found in Appendix 1) and grade 3/4 AEs, respectively. 1 patient (2%) died due to sepsis, which was deemed treatment-related; 4 more deaths (7%) were not deemed treatment-related.

Charlton[180] reported a prospective, multicentre, open-label pilot study, which enrolled 40 patients with compensated recurrent HCV infection of any genotype after a primary or secondary liver transplantation. All patients received 24 weeks of SOF + RBV (starting at 400 mg daily, which was adjusted according to creatinine clearance and haemoglobin values). The most common AEs were fatigue (30%), diarrhoea (28%), and headache (25%). Anaemia was reported in 20% of patients. Two patients (5%) discontinued study treatment due to AEs, which were considered unrelated to study treatment. No deaths, graft losses, or episodes of rejection occurred. No interactions with any concomitant immunosuppressive agents were reported.

LDV+SOF+RBV

Charlton[176] was an open-label study conducted at 29 sites in the US. Patients either had a HCV genotype 1 infection (99%) or a HCV genotype 4 infection (1%). Patients were treated in 7 different groups, for either 12 or 24 weeks. Patients in Cohort A were patients with advanced cirrhosis and had not undergone liver transplantation; patients in Cohort B had previously undergone liver transplantation. Overall, 169 pre- and post-transplantation patients received SOF+LDV+RBV for 12 weeks, and 168 pre- and post-transplantation patients received SOF+LDV+RBV for 24 weeks. In four out of seven treatment groups, the starting dose of RBV was 600 mg daily.

98% of patients in each group experienced any AE; the most common AEs were not reported. 2% and 5% of patients in the 12-week-group and the 24-week-group discontinued treatment due to an AE. While 31% in the 24-week group experienced SAEs, 15% of patients in the 12-week-group had SAEs. Grade 3/4 AEs were not reported. In total, 4% of patients died during the study, however, none of the deaths was deemed treatment-related.

SMV+SOF with/without RBV

Punzalan[178] was a prospective, observational study. Treatment-naive and treatment-experienced post-transplantation patients (for HCV genotype 1 infection) with or without cirrhosis received SMV+SOF for 12 weeks (n=42).

Pungpapong[179] was a multi-centre study conducted in the US. Overall, 123 post-transplantation patients with HCV genotype 1 infection received SMV+SOF with or without RBV for 12 weeks. Overall, 20% of patients received RBV. RBV dosing was weight-based, at the discretion of the treating physicians; the initial dose was based on the estimated glomerular filtration rate and ranged from 200 mg to 1200 mg per day.

Across the two studies, 33% and 48% of patients experienced any AE. The most common AEs in Punzalan[178] were rash (12%), aminotransferase increase (7%), and others (about 2% each), such as confusion, pulmonary embolism, clostridium difficile, fatigue, shingles, pneumonia, edema, and joint pain. The most frequent AEs in Pungpapong[179] were anaemia in the RBV group (72%; vs 5% in patients not receiving RBV, P<0.001), fatigue (13%), skin complaints (6%) and others (5% each), such as headache or gastrointestinal complaints. In Pungpapong[179] 3 patients (2%) discontinued treatment due to an AE, however, in one patient with acute pancreatitis treatment was restarted after 2 weeks; in Punzalan[178]there were no treatment discontinuations. Punzalan[178] did not report on SAEs or grade 3/4 AEs. Furthermore, the authors stated that there was no death. However, one death occurred four months after finishing a full treatment course and was thought not to be related to HCV medication. In Pungpapong[179] 3 patients (2%) experienced SAE, including death (pneumonitis), acute pancreatitis, and acute kidney injury (obstructive ureteral stone). Grade 3/4 AEs were not reported. There was one death during the study, possibly due to drug-induced lung injury.

OBV+PTV+RIT+DSV+RBV

Kwo[177] CORAL-I was a single-arm, open-label trial. 34 post-transplantation patients with a HCV genotype 1 infection without cirrhosis received OBV+PTV+RIT+DSV+RBV for 24 weeks. RBV dosing was at the investigator's discretion.

97% of patients reported any AE; the most frequent were fatigue (50%), headache (44%), cough (32%), anaemia (29%), diarrhea, and insomnia (26% each). 1 patient (3%) discontinued treatment due to an AE. 2 patients (6%) experienced SAE, including hypotension and tachycardia in 1 patients (possible drug-drug interaction with tamsulosin), and peripheral edema and neuropathic pain in a lower extremity in 1 patient. The authors did not report grade 3/4 AEs or deaths.

In conclusion, treatments with SOF+RBV, LDV+SOF+RBV and SMV+RBV were well tolerated in pre- or post-liver transplantation patients; the most frequent AEs were fatigue, diarrhoea, headache, and anaemia. The same was not true for the OBV24+PTV24+RIT24+DSV24+RBV24 treatment regimen, reported by Kwo[177]. In this study, AEs were reported by the majority of patients (97%), with the most common being fatigue (50%), headache (44%), cough (32%), anaemia (29%), diarrhoea (26%), and insomnia (26%), but SAEs were rare.

Table 6.6. provides a summary of several AE categories.

Table 6.6. Any AEs, the most frequent AEs, SAEs, discontinued treatment due AEs with six DAAs under assessment, in regimens without IFN, with pre- or post-liver transplantation patients [176-181]

Drug combination and studies	Any AEs N (%)	The most frequent AEs (%)	SAEs N (%)	Discontinued treatment due AEs n (%)
SOF				
Curry et al. (2015)[181]: SOF48+RBV48 before liver transplantation	54 (89)	fatigue (38), headache (23), anaemia (21)	11 (18)	2 (3)
Charlton et al. (2015) [180]: SOF24+RBV24	39 (98)	fatigue (30), diarrhoea (28), headache (25), anaemia (20)	6 (15)	2 (5)
LDV+SOF				
Charlton et al. (2015)[180] SOLAR 1 study: SOF12+LDV12+RBV 12;	166 (98); 165 (98)	NR	52 (31)	9 (5)

SOF24+LDV24+RBV 24				
SMV				
Punzalan et al. (2015)[178]: SMV12+SOF12	14 (33)	rash (12), aminotransferase increase (7.1); confusion, fatigue, pulmonary embolism, clostridium difficile, shingles, edema, joint pain (2.4)	NR	0
Pungpapong et al. (2015)[179]: SMV12+SOF12; SMV12+SOF12+RBV12	59 (48)	anaemia (72 RBV group), fatigue (13), rash/pruritus/photosensitivity (6); each (5) headache, nausea/diarrhea, anemia (non-RBV group)	3 (2)	3 (2)
OBV+PTV+RIT+DAS				
Kwo et al. (2014)[177] CORAL-I study: OMB24+PAR24+RIT 24+DAS24+RBV24	33 (97)	fatigue (50), headache (44), cough (32), anaemia (29), diarrhoea (26), insomnia (26)	2 (6)	1 (3)

12 = 12 weeks; 24 = 24 weeks; 48 = 48 weeks; AE = adverse event; DAA = direct-acting antiviral; DAS = dasabuvir; DCV = daclatasvir; IFN = interferon ; LDV = ledipasvir; OMB = ombitasvir; PAR = paritaprevir; RBV = ribavirin; RGT = response-guided therapy; RIT = ritonavir; SAE= serious adverse event ; SMV = simeprevir; SOF = sofosbuvir

[B0010] What kind of data/records and/or registry is needed to monitor the use of the new treatments (sofosbuvir; ledipasvir + sofosbuvir; simeprevir; daclatasvir; ombitasvir + paritaprevir + ritonavir; dasabuvir) and the comparators?

EPAR and SmPC were used to answer “what kind of data/records and/or registry is needed to monitor the use of the new DAA treatments and the comparators”. Details of the risk management plan (RMP) for the new DAA treatments under assessment and the comparators could be found in Appendix 1.

New oral DAA treatments under assessment

Sofosbuvir

An RMP has been developed to ensure that sofosbuvir is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for sofosbuvir, including the appropriate precautions to be followed by healthcare professionals and patients.

Ledipasvir/sofosbuvir

An RMP has been developed to ensure that sofosbuvir + ledipasvir is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Simeprevir

Limited information exists on the use of simeprevir in combination with medicines for HCV other than PR, in patients greater than 65 years old or previously treated with another direct-acting HCV medicine (such as boceprevir and telaprevir).

No information exists for patients less than 18 years old, pregnant or breastfeeding women, patients with moderate to severely impaired liver function or kidney disease, patients coinfected with HBV, and those who have received or are eligible for an organ transplant.

Daclatasvir

Further studies are being conducted to evaluate daclatasvir in combination with other antiviral medicines, particularly sofosbuvir, to find out more about its effectiveness in all HCV genotypes and in patients whose previous treatment with peginterferon has failed, in patients with cirrhotic livers before and after liver transplantation, and in patients infected with both HCV and HIV. In addition, the duration of benefits of daclatasvir resistance to treatment, and the progression of liver disease in patients treated with daclatasvir are currently being investigated.

Ombitasvir/paritaprevir/ritonavir

An RMP has been developed to ensure that ombitasvir + paritaprevir + ritonavir is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet for ombitasvir + paritaprevir + ritonavir, including information on the appropriate precautions to be followed by healthcare professionals and patients.

This medicine has no additional risk minimisation measures.

Dasabuvir

There is limited information available on the use of dasabuvir in patients greater than 65 years of age, in patients who have had a liver transplant, and in patients also infected with HIV-1.

No information exists for patients less than 18 years of age, patients with moderate to severe liver impairment or kidney disease, patients also infected with HBV, and chronic HCV infection patients with genotype 4 who have cirrhosis. Further studies are being conducted to find out more about the effectiveness of dasabuvir with ombitasvir + paritaprevir + ritonavir in these patients. No information is available on the use of dasabuvir with ombitasvir + paritaprevir + ritonavir in combination with HCV medicines other than ribavirin, or use of dasabuvir with ombitasvir + paritaprevir + ritonavir in patients whose previous treatment with another direct-acting HCV medicine (such as boceprevir, telaprevir, sofosbuvir, or simeprevir) had failed. There are no data on use of dasabuvir with ombitasvir + paritaprevir + ritonavir in pregnant or breastfeeding women.

6.3. Discussion

In this relative safety assessment, there were no randomised or other studies that directly compared the second generation DAA oral therapies (head-to-head studies). The majority of studies compared different dosing regimens of the same drug combinations to each other but not to older therapies like PR or PR plus one of the first generation protease inhibitors. The lack of head-to-head clinical trials and only single-arm studies makes it difficult to compare the safety of the different treatment regimens. Data for genotypes 5 and 6 were insufficient for any conclusions. Data were limited for patients with HIV coinfection and post-transplanted patients.

Interferon-containing regimens for genotype 1 HCV infection

The Canadian SR with NMA[13], assessing 4 DAAs (boceprevir, telaprevir, SOF, and SMV) in combination with PR, in comparisons with PR alone, in patients with genotype 1 chronic HCV infection, identified 3 key AEs: anaemia, depression, and rash. These events were analysed using NMA methods. The findings for treatment-naive and treatment-experienced patients were similar; comparative data for SOF were available for treatment-naive patients only.

The risk of anaemia was statistically significantly higher for patients who received boceprevir or telaprevir compared with PR alone, but not for SMV+PR or SOF+PR versus PR alone, based on both direct pairwise and indirect comparisons. The absolute risk of anaemia was higher for telaprevir or boceprevir versus SMV, but the differences did not consistently reach statistical significance.

No statistically significant differences were detected between boceprevir, telaprevir, SMV, or PR alone regarding the risk of depression for both treatment-naive and treatment-experienced patients, in both direct and indirect analyses. No comparative data were available for SOF.

Among treatment-naive patients, telaprevir was associated with a statistically significant increased risk of rash versus PR alone based on direct pairwise comparisons; however, these differences were no longer statistically significant in the NMA. No other direct or indirect treatment comparisons showed statistically significant differences for rash in treatment-naive patients. Among treatment-experienced patients, there was a statistically significant increased risk of rash for patients who received boceprevir or telaprevir compared with PR alone, based on direct and indirect evidence. Some comparisons between the different dosage regimens of boceprevir or telaprevir versus SMV showed a lower risk of rash for those receiving SMV; however, the differences were not consistently statistically significant.

No clear increased risk of the SAEs influenza-like symptoms or neutropenia were observed among patients who received DAA plus PR, compared with PR alone. Pruritus and anorectal discomfort were reported more frequently among patients who received telaprevir than PR alone. Suicidal ideation was infrequently reported, and no conclusions can be drawn for this AE[13].

In our update of the Canadian SR, the findings for treatment-naive, treatment-experienced, and combined patients on SMV, in combination with PR, for genotype 1 HCV infection were similar in terms of the AEs reported; the overall AE profile in SMV-treated patients in combination with PR was comparable to that in patients who received PR alone. The most frequent AEs in both groups were neutropenia, anaemia, rash, and pyrexia. The rates of discontinuations due to AEs were similar for both the SMV+PR group and the PR alone group; the same was true for SAEs. No new comparative data were available for SOF+PR versus PR alone.

In the only one head-to-head study found, the ATTAIN study, Reddy[162] differences were recorded between treatment groups in SMV- or telaprevir-related AEs (69% in the SMV+PR group vs 86% in the telaprevir+PR group), SAEs (2% vs 9%), and AEs leading to study drug discontinuation (2% vs 8%).

No new comparative data were available for SOF+PR versus PR alone.

A limitation of these studies is that important patient populations were excluded, such as HIV- (except Dieterich[168] on SMV) and hepatitis B virus (HBV)-coinfected patients, liver transplanted patients, and those with decompensated liver disease.

According to the SR and meta-analysis published by Institute for Clinical and Economic Review[207], which reviewed the comparative clinical effectiveness of 4 oral DAA combination therapies in genotype 1 chronic HCV infection: SMV+SOF, LDV+SOF, DCV+SOF, and OBV+PTV+RIT+DSV+RBV, as well as 3 single DAA regimens with/without PR: SMV+PR, SOF+RBV, and SOF+PR, there were very few discontinuations from therapy in any of the studies due to AEs, and the rate of SAEs was similarly low. When patient characteristics required longer therapy with RBV-based therapy (SOF+RBV for 24 weeks, OBV+PTV+RIT+DSV+RBV for 24 weeks), the AE rates were higher (e.g., the rate of significant anaemia was higher, SMV also caused photosensitivity and more rashes).

The combinations that include RBV have an increased incidence of anaemia, particularly when taken for 24 weeks or when combined with IFN. The combinations that include SMV are associated with a greater incidence of rashes. The elimination of IFN from the treatment regimen decreases the risk for several AEs including fatigue, headache, flu-like illness, anaemia, pruritus, nausea, and rashes. There were also significantly fewer grade 3 or 4 AEs, when those were reported[207].

Interferon-containing regimens for genotypes 2 to 6 HCV infection

Frequency of any AEs reported with three DAAs + PR regimen in genotypes other than genotype 1 (SOF, 4 clinical studies[1,154,163], one with HIV coinfection[172]; one in SMV[166] and one in DCV[165]) was within the range of 70%-99%, SAEs were reported with a frequency of 5%-9%. The most frequent AEs across all studies were headache, fatigue, and insomnia and in HIV confection patients anemia and neutropenia (52%-57%).

Interferon-free regimens for genotype 1 to 6 HCV infection

Data reported in our rapid REA showed that IFN-free therapies were better tolerated than treatment regimens with PR. With six DAAs under assessment, in regimens without IFN, frequency of any AEs reported was within the range of 40%-100%.
Discontinuations due to AEs were reported infrequently. SAEs were reported with frequency of 1%-10%. The most common AEs reported for the new oral drugs under assessment (in treatment-naive, treatment-experienced, and combined patient groups) were headache, fatigue, insomnia, and nausea. In treatment regimens with PR, the most common AEs were rash, neutropenia, and anaemia.

In one study[150], on OBV12+PTV12+RIT12+DSV12, with or without RBV, AEs of pruritus, nausea, and insomnia occurred at a statistically higher frequency among patients who received RBV than among those who did not (P=0.02). This was also the case for low haemoglobin levels.

In one study[152] on OBV12+PTV12+RIT12+DSV12, with or without RBV, fatigue, nausea, insomnia, anemia, rash, increased blood bilirubin levels, and low haemoglobin levels occurred at a statistically higher frequency among patients who received RBV than among those who did not (P<0.001-0.017).

In one study[144] on OBV+PTV+RIT+DSV+RBV for 12 or 24 weeks, fatigue and dyspnoea were statistically significantly higher in the 24-week group than in the 12-week group.

Safety profile was not related to dosage or frequency of administration for the majority of new DAAs under assessment. Also, for the majority of combinations, the frequency of AEs did not change over the observed time period of 12 or 24 weeks, for the majority of combinations. The only statistically significant difference was found for the combination of OBV+PTV+RIT+DSV+RBV in the TURQUOISE-II study[144]. Fatigue and dyspnoea were statistically significantly higher in the group of patients treated for 24 weeks than in those treated for 12 weeks. In the ION-2 study[146], among patients who received LDV–SOF without RBV, the incidence of AEs was higher in the 24-week group than in the 12-week group (81% vs 67%).

With regards to the susceptible patient groups that are more likely to be harmed, only a few studies were found in HIV-coinfected[168-172,174,175] and pre- or post-liver transplanted patients.[176-181]
AEs were common with HIV coinfection, ranging from 70% to 100%. The most common AEs were fatigue, insomnia, and headache, for studies on SOF+RBV and SOF+LDV.[169-171] For studies on SOF12+PR12 and SMV12+PR24/48 RGT, the most common AEs were fatigue, headache, nausea, neutropenia, and anaemia[168,172]. More patients discontinued treatment due to AEs in treatment regimens with PR. For the study on DCV12+SOF12, the most frequent AEs were fatigue (17%), nausea (13%), and headache (11%)[175]; for studies on OBV+PTV+RIT+DSV+RBV the most common AEs were fatigue, insomnia, nausea, and headache[174].

Treatments with SOF+RBV, LDV+SOF, and SMV+RBV were well tolerated in the few published studies in pre- or post-liver transplantation patients[176,178-181]; the most common AEs being fatigue, diarrhoea, headache, and anaemia[176,178-181]. The same was not true for the OBV24+PTV24+RIT24+DSV24+RBV24 treatment regimen reported by Kwo[177]. In this study, AEs were reported by the majority of patients (97%), with the most common AEs being fatigue (50%), headache (44%), cough (32%), anaemia (29%), diarrhoea (26%), and insomnia (26%), but SAEs were rare.

According to the literature data and SmPCs, liver transplant recipients, patients with decompensated cirrhosis, HIV/HCV-coinfected patients, and renally impaired patients are the susceptible patient groups that are more likely to be harmed with the new treatments. The lack of clinical study safety data are evident for children and adolescents less than 18 years of age, pregnant women, and women during the lactation period[208]. The potential drug-drug interactions should be carefully evaluated; recently in post-marketing AEs surveillance, reports of symptomatic bradycardia were reported on LDV/SOF in co-administration with amiodarone[209].

According to a review by Kwo[210] of clinical trials in transplant settings on drug options in patients with decompensated cirrhosis, and drug options in end-stage renal disease, SOF+LDV may be safely administered with calcineurin inhibitors (tacrolimus, cyclosporine) and rapamycin inhibitors (sirolimus, everolimus). PTV, RIT, OBV, and DSV may be administered with tacrolimus and cyclosporine, although appropriate dose adjustments must be made to the calcineurin inhibitors. In patients with decompensated Child's Class B/C cirrhosis, SOF, LDV+SOF as well as DCV may be given without dose adjustment. In renal impairment, all DAAs may be used safely down to a glomerular filtration rate

(GFR) of 30 mL/min. SMV, PTV, OBV, and DSV may be given to patients with a GFR of 15 mL/min. DCV may be given without dose administration change. The authors concluded that DAAs have better tolerability and greater efficacy than IFN-based therapy post-transplantation.

According to Cholongitas[211], both liver transplant candidates and recipients can now be safely and effectively treated, which was not true in the pre-DAAs era. Today, there is no controversy on the use of the IFN-free regimens in liver transplant candidates and recipients. The most important clinical dilemma is still the need for therapeutic intervention in liver transplant candidates with very advanced liver disease, mostly Child's Class C cirrhosis. The therapeutic regimens should be carefully selected in this setting because of possible complications and the frequent use of other medications. HCV genotypes, liver and renal function, and co-medications should be always taken into account.

We would like to stress the slightly different grading system of AEs used in the US[212] and Europe[213], which did not allow a precise count of the SAE rate due to some overlapping of SAEs and grade 3 AEs (consisting of severe AEs and SAEs) in the US grading system (grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; grade 2: Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living; grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living; grade 4: Life-threatening consequences; urgent intervention indicated; grade 5: Death related to AE)[212,213].

The EUnetHTA guideline[213] clearly distinguishes severe and serious AEs: severe relates to intensity, while a serious adverse reaction results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect, and is a medically important event or reaction. In this report we have used both terminologies (SAE and grades 3-4), as used in the published articles cited.

A limitation of our relative safety assessment is that we used published articles of RCTs or prospective studies as a primary source for data extraction. Recent publications again stressed insufficient information from clinical trials in journal publications and results posted in clinical trial registries, however, these could supplement each other to overcome publication and outcome reporting bias. Full clinical study reports provide the most complete information on the large majority of methods and results data items; HTA doers should rely on systematic review of full clinical study reports when they become publicly available to solve the problem of overestimating benefits and underestimating harms[214-217].

Pragmatic randomised head-to-head trials or high-quality observational studies from real-world settings with larger numbers of patients will be essential for evaluating the comparative safety of the combination DAA therapies or to identify possible rare AEs. More studies are needed for liver transplant recipients, patients with decompensated cirrhosis, HIV/HCV-coinfected patients, and renally impaired patients. None of the DAAs are free of drug interactions. Careful management of drug interactions is critical to minimise AEs in these populations. Post marketing surveillance, including spontaneous AEs reporting will help to recognize full safety profile of new DAAs; different new SAEs, some as consequence of drug-drug interactions, are already reported, as presented in domain "Description and technical characteristics of the technology" of this rapid REA report.

7 POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL, AND LEGAL ASPECTS

7.1. Research questions

Table: Checklist for potential ethical, organizational, social and legal aspects

This checklist will assess whether the domains not included in a rapid REA (i.e. the ethical, organizational, social, and legal domains) could be relevant for the topic of this pilot. If deemed appropriate, the users of the final report can address these issues on a national level. The table also presents potentially relevant assessment elements from the HTA Core Model from these domains, to provide guidance for the user on a national level.

Table 7.1. Checklist for potential ethical, organizational, social and legal aspects

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	Yes
Various issues similar to those seen when ARV was introduced for HIV may emerge[218]. For example, effective and safe treatment of hepatitis C in people who inject drugs (PWIDs) may be regarded as a new way of prevention of disease spread, i.e. treatment as prevention[218-220]. Potential non-use of new compounds due to the high price may also be a potential aspect in general population and in particular for PWIDs in some countries. EASL 2015 guidelines provide a list stating populations which should be prioritized[34]. Although they give individuals at risk of transmitting HCV a priority, guidance in individual European countries is not always clear[221]. Further subpopulation to take into account is people in prisons[222]. Relevant questions: F0003 Are there any other hidden or unintended consequences of the technology and its applications for patients/users, relatives, other patients, organisations, commercial entities, society, etc.? F0012 How does implementation or withdrawal of the technology affect the distribution of health care resources? F0013 How are technologies with similar ethical issues treated in the health care system? H0012 Are there factors that could prevent a group or person from gaining access to the technology?	
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators require organisational changes?	Yes
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	Yes
More effective and safe treatments, together with possible increase in public awareness may lead to	

identification of a greater proportion of people who are currently asymptomatic and undiagnosed, leading to an increase in patient flow. The cascade of care for people who were screened positive for hepatitis C, although still not fully conceptualised, includes '1. obtaining HCV screening results; 2. being linked to HCV care; 3. receiving diagnostic test results; 4. deciding on and initiating HCV therapy; 5. adhering to and completing HCV therapy'[223]. Clinical and individual level barriers to HCV treatment among general population may emerge, and also among some subpopulations, which may need additional multidisciplinary care, for example PWID or patients on haemodialysis[34,224].

Relevant questions:

G0001 How does the technology affect the current work processes?

G0100 What kind of patient/participant flow is associated with the new technology?

G0004 What kind of cooperation and communication of activities have to be mobilised?

G0101 What are the processes ensuring access to care of the new technology for patients/participants?

G0009 Who decides which people are eligible for the technology and on what basis?

3. Social	
3.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	Yes

There is still low awareness of the disease in general population, as well as misconceptions about treatment possibilities, which prevents people from getting tested. On the other hand, patients aware of their status who have deferred treatment for various reasons, in particular because of side effects, may decide to undergo treatment now. Less side effects may result in patients being able to go to work during treatment, which may have an impact at societal level. Social factors and support seem to be very important for PWIDs[224].

Relevant questions:

H0003 What kind of support and resources are needed for the patient or citizen as the technology is introduced?

H0006 How do patients, citizens and the important others using the technology react and act upon the technology?

H0011 What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?

H0009 What influences patients' or citizens' decisions to use the technology?

4. Legal	
4.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	No

7.2. Main results

Potential ethical aspects

Research questions

Element ID	Research question
F0003	Are there any other hidden or unintended consequences of the technology and its applications for patients/users, relatives, other patients, organisations, commercial entities, society, etc.?
F0012	How does implementation or withdrawal of the technology affect the distribution of health care resources?
F0013	How are technologies with similar ethical issues treated in the health care system?
H0012	Are there factors that could prevent a group or person from gaining access to the technology?

[F0003] Are there any other hidden or unintended consequences of the technology and its applications for patients/users, relatives, other patients, organisations, commercial entities, society, etc.?

The current cost of the new pharmaceuticals for the treatment of chronic hepatitis C is very high. It seems to be high for many health care systems. Even if over time the price of the new drugs will be reduced through competition and eventual patent expiration, the issue of access to treatment will be challenging.

This means that less patients than needed will be treated; or at least that many patients will be forced to defer effective treatments (this requires extra policies, the so-called “informed deferral” policies)[225]. Therefore, unintended consequences may result in several forms of inequities in access to treatment. In turn, these inequalities to treatment access may cause: a higher number of deaths; more physical and psychological pains; a higher number of conflicts between patients and/or health care systems/physicians; economic speculation; medical tourism to countries that provide the drugs at lower cost.

[F0012] How does implementation or withdrawal of the technology affect the distribution of health care resources?

The current cost of the new pharmaceuticals for the treatment of chronic hepatitis C is very high. Their implementation will require optimization of the resources by the Health Care Systems.

The following are points around how implementation of the new pharmaceuticals for the treatment of chronic hepatitis C may affect the distribution of health care resources:

1. The need for IFN-free combination regimens with two or more DAA for most of the patients and longer treatment duration for patients with cirrhosis may cause an increase of costs;

2. Chronic hepatitis C is a systemic condition: it is strongly associated with other pathologies such as diabetes, cardiovascular disease, psychiatric disorders, renal dysfunction, and rheumatologic conditions. Hence, not only liver-related clinical outcomes, but also extra-hepatic complications have to be considered[226]. In this sense, it is necessary to think not just in terms of mere price of the drugs.

3. Data on treatment referral are not so clear. In addition, evidence indicates that disease progression is not linear in chronic hepatitis C[227]: recent analyses have showed that rates of fibrosis progression may be more accelerated than previously thought [197]. A treatment

deferral could thus run the risk to allow progression to cirrhosis for a subset of patients, therefore increasing their future risk of hepatic decompensation or hepatocellular carcinoma[226]. The problem becomes more evident for patients with minimal or mild fibrosis, as the specific risk factors for disease progression have not been clearly defined yet, thus not allowing to have certain indications regarding the precise benefit and optimal timing of antiviral therapy in patients with early-stage disease. All these elements may affect the distribution of health care resources.

4. Legal conflicts between patients and/or health care systems/physicians may increase costs for the relative country/region.

[F0013] How are technologies with similar ethical issues treated in the health care system?

Similar ethical issues arose with the implementation of HAART - an effective combination anti-retroviral therapy that delays the onset of AIDS.

The emergence of competition from generic manufacturers, direct negotiation with pharmaceutical companies and activist pressure have all contributed to a dramatic drop in the price of these pharmaceuticals to treat AIDS[228].

In 1996, HAART became available to those living with HIV in rich countries. Within 4 years, death rates caused by HIV-related illnesses in developed countries dropped by 84%.

At the beginning of 2000 an Indian pharmaceutical company started to produce generic antiretrovirals that were exactly the same as those made by large pharmaceutical companies, but significantly cheaper. This sparked a “price war” between branded and generic drug makers, which forced the large pharmaceutical companies to lower the price of their AIDS drugs. This competition, coupled with pressure from activists, organisations - such as the Clinton Foundation - and governments dramatically reduced the price of HAARTs.

Around the world today, health policy still restricts access to these drugs to varying degrees. Only 10 countries have formally adopted the option for people diagnosed with HIV to start antiretroviral treatment immediately. Many countries have not fully implemented WHO recommendations[229] to start antiretroviral treatment for people living with HIV. Some countries still require people to wait before becoming “eligible” for antiretroviral treatment. Only three countries (the US, Thailand, and Malaysia) are currently implementing pre-exposure prophylaxis[230].

[H0012] Are there factors that could prevent a group or person from gaining access to the technology?

These are the factors that could prevent a group or person from gaining access to new pharmaceuticals for the treatment of chronic hepatitis C.

Resource barrier: due to lack of resources some heath care institutions may make the access to treatment not available for many patients. Therefore, provision of the drugs will depend on available economic resources of the relative health care systems.

Financial barrier: If a patient has to pay for medical prescriptions they may not be able to afford it. If a patient lives in a country/region where there is no provision they may not be able to afford transport costs.

Geographical and political barrier: access to treatment may differ across regions/countries. A patient may need to have the treatment, but its accessibility may be many miles away or not possible for political reasons.

Diagnostic barrier: To date it is estimated that more than 90% of HCV infected individuals worldwide are unaware of their HCV positive status, also due to the fact that chronic hepatitis is asymptomatic until the developments of late-stage cirrhosis or hepatocellular carcinoma[231]. Therefore lack of diagnosis could prevent a group or person from gaining access to the drugs **(A0004, A0005, A0024)**.

See also **(G0101)**.

Discussion

The implementation of the new pharmaceuticals for the treatment of chronic hepatitis C is currently facing cost and access issues. Less patients than needed are currently treated and many patients are forced to defer effective treatments.

Irrespective from real effectiveness of these new drugs, health systems in many countries are facing a huge problem of distributive justice. While these should guarantee individual rights, among which the right to health - in its broader sense that is not limited to healing, but extended to quality of life - they also have to grant equal access new therapies

Surmounting it will require collaboration among healthcare providers, drug manufacturers, local and national governments, and other stakeholders.
Most urgently there is a need to consider ethical issues linked to access to new therapies and to eligibility criteria. In a setting of restricted access, the selection of patients for immediate treatment or deferral entails strict adherence to established, validated and ethically accountable policies[232].

Potential organisational aspects

Research questions

Element ID	Research question
G0001	How does the technology affect the current work processes?
G0100	What kind of patient/participant flow is associated with the new technology?
G0004	What kind of cooperation and communication of activities have to be mobilised?
G0101	What are the processes ensuring access to care of the new technology for patients/participants?
G0009	Who decides which people are eligible for the technology and on what basis

[G0001] How does the technology affect the current work processes?

European clinical guidelines **(A0025)** identified prioritization criteria for HCV treatment. At the same time for defined subgroups of patients (with or without cirrhosis, retreated, pre or post liver transplant) specifies all alternative treatment that could be prescribed. Among treatments the technologies under assessment are included.

National clinical guidelines **(A0025)** consider or are under revision to include technologies under assessment. The updating process of national guidelines is linked to national negotiating processes.

A positive impact of medical management of HCV-related complications with new DAAs could be expected. One of the most significant ones will be in terms of avoided liver transplants due to higher efficacy of new treatments.

Studies on the impact of HCV treatment on liver transplantation activity have been published considering comparators of the current assessment. In the study of Dueffic-Burban[233] progression of yearly-HCV-infected cohorts was simulated and 2013–2022 candidates for liver transplantation without and with therapies were calculated. Dual and triple therapies were considered. In France[233] current treatment would avoid transplantation of 4425 (4183–4684) potential candidates during the period 2013–2022.

[G0100] What kind of patient/participant flow is associated with the new technology?

For the patient the use of technologies under assessment does not cause any additional steps in the management.

Treatment should be initiated and monitored by a physician experienced in the management of patients with HCV. Drugs are administrated orally.

[G0004] What kind of cooperation and communication of activities have to be mobilised?

Specific access to care programs should be effectively communicated to:

- Pharmaceutical companies.
- Patients.
- Patients/citizens associations.
- Health personnel.
- General public.

Communication should focus on defined criteria to access and motivations that lead to their selection, as long-term sustainability of HCV treatments.

These stakeholders could be involved in the elaboration of a wider HCV national policy **(G0101)**.

[G0101] What are the processes ensuring access to care of the new technology for patients/participants?

There are several reasons of no treatment in patients who fulfil the treatment indications. Data on barriers to management for chronic HCV patients in Europe[234] helped to identify the main reasons of no treatment in clinical, economical, and organizational ones:

- Medical contraindications to interferon alpha-based therapy (or other HCV therapies).
- Patients' refusal for interferon alpha-based therapy (or other HCV therapies).
- Lack of patient HCV awareness and education **(H0009)**.
- Non-adherence.
- Loss to follow-up.
- Older age.
- Non-advanced fibrosis at liver biopsy.
- Active parenteral drug users (PDU).
- Alcohol abuse.
- Geographical area of residence. The distance from the nearest practitioner, practitioner's competencies and staffing capacity impact on the access to appropriate care.
- Lack of financial resources. The importance of cost emerged with the first-generation protease inhibitors (boceprevir, telaprevir) and is expected to play a crucial role with new DAAs.

Cost and access are now the main hurdles to be overcome in HCV treatment.

Access to care programs for new DAAs could be influenced by:

- **Prioritization criteria** defined at national level. They allow to give early access to care to patients with the highest burden of care and/or to high risk HCV population. These criteria reflect national/local HCV epidemiology and take into account logistical and economic conditions.

- **The need to monitor both the utilization and effectiveness** of intervention as well as the evolution of HCV. There are high expectations for these curative treatments. The risk is that, despite the availability of a curative treatment, it remains accessible only to the most severely ill patients and hence this transmissible disease will continue to drive new infections. Therefore, eradication of HCV is not guaranteed.

- **Financial agreements** between regulators and producers on prices. In countries with high prevalence/incidence rate the economic impact must be monitored and managed. Possible solutions are: price-volume agreements, drug expenditure caps, etc.

- **HCV health policies**. The definition or update of a strategic plan for the management of hepatitis C could help to coordinate all aspects involved by these new drugs. Indeed, a balance between risk-benefit profiles, cost-effectiveness, added values of new drugs, and long term sustainability of HCV burden of care should be found. Then, an estimate of the capacity of the health system to treat patients should be done. A HCV dedicated budget could be a further political tool to consider.

Access to care programmes for the technologies under assessment should be based on:

- **Identification of target population**. Evaluation of epidemiological data is the starting point. It is necessary to know the number of patients already on treatment and the likely number undiagnosed **(A0007)**.

- **Identification of the patients that should be treated first**. This is often present as a choice between treating people who are most likely transmit the virus on one hand or trying to identify people with advanced fibrosis and treating them before their liver decompensates on the other.

- **Identification of prescribing centres** that will be specialized in treatment and follow-up of HCV-infected patients. For example, the Strategic Plan for the Management of Hepatitis C in the National Spanish Healthcare System[235] defines the criteria for these centres.

In Georgia, an HCV eradication program summarizing most of these elements is underway. In fact, the key strategies of Georgia's nationwide hepatitis C elimination program[236] are:

- Improved treatment access.

- Secure political commitment.

- Partnership development engaging international public health, academic, and industry partners. The partnership is involving Gilead Sciences, a pharmaceutical manufacturer that agreed to support the program by providing an initial 5,000 courses of the antiviral medications sofosbuvir, followed by 20,000 treatment courses of ledipasvir/sofosbuvir annually at no cost.

- Capacity assessment evaluating national HCV epidemiology and laboratory and health care capacity.

- National planning.

- Monitoring and evaluation.

- Provider education.

- Defining disease burden with a national seroprevalence survey.

- Raising awareness with national communication campaigns.

A further example is the Strategic Plan for the Management of Hepatitis C in the National Spanish Healthcare System[235]. Its actions are:

- Design and implementation of a national registry of HCV patients treated with antivirals.
- Production of a Guide of Recommendations for Early Diagnosis of HCV Infection in Priority Groups within Primary Care. In addition it defines a program aimed to enhance prevention and diagnosis of HCV infection within Penitentiary Institutions.
- Production of a Clinical Care Guideline for HCV.
- Updating protocols for biological hazards prevention among healthcare professionals, improving surveillance of HCV-infected staff.
- Characterization of the centres that will be specialized in treatment and follow-up of HCV-infected patients with allocation to these centres of physicians with experience in chronic HCV and cirrhosis, who have used previously oral antiviral pharmaceuticals in their clinical practice.
- Inclusion of candidates to liver transplants into a Transplant Program. Patients with decompensated cirrhosis who are potential candidates to liver transplants are assigned to III and IV level hospitals.
- Assure availability of devices and infrastructure for:
    - Transient elastography (FibroScan).
    - Abdominal ultrasound.
- Assure accessibility to:
    - Rapid (<1 week) detection of RNA-HCV.
    - Interleukin (IL) 28B genotype test.
    - Q80K polymorphism screening.

[G0009] Who decides which people are eligible for the technology and on what basis?

National and regional authorities are entitled to define criteria to identify eligible people and to implement those decisions. A coordinated effort by national and local authorities is requested.

On the base of characteristic of each Health System the most appropriate authority is defined. Combining price negotiation, prioritization criteria, and identification of treatable patients could be an effective solution.

Identification of eligible population could be part of a wider HCV policy **(G0101)**.

Discussion

Interventions under assessment could impact on current work processes **(G0001)** due to:

- Prioritization criteria in treating HCV patients defined my clinical guidelines **(A0024, A0025)** or HCV health policies.
- Clinical guidelines recommendations **(A0025)** in terms of which therapy option adopt for different patients.
- Their impact on the evolution of HCV. A higher efficacy could have impact on the use of health services. An indirect impact is an expected lower rate of liver transplants among HCV patients treated with new DAAs.

For the patient, the use of technologies under assessment does not cause any additional steps in the management **(G0100)**.

Barriers to care and treatment should be investigated before to define an appropriate access plan **(G0101)**. They could be clinical, economical, and organizational ones.

Access to care programmes for the technologies under assessment should be based on **(G0101)**:

- Identification of target population.
- Identification of the patients that should be treated first.
- Identification of prescribing centres.

Specific access to care programs should be effectively communicated among different stakeholders **(G0004)**.

National and regional authorities are entitled to define criteria to identify eligible people and to implement those decisions. A coordinated effort by national and local authorities is requested **(G0009)**.

Potential social aspects

Research questions

Element ID	Research question
H0003	What kind of support and resources are needed for the patient or citizen as the technology is introduced?
H0006	How do patients, citizens and the important others using the technology react and act upon the technology?
H0011	What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?
H0009	What influences patients' or citizens' decisions to use the technology?

[H0003] What kind of support and resources are needed for the patient or citizen as the technology is introduced?

Introduction of the technology should be part of interdisciplinary HCV management programs that include actions aimed to patients and providers, as well as at the health system and social level[237]:

- *Identification of all persons with hepatitis C*, by means of effective hepatitis C testing programs, especially to high prevalence populations. Positive results for HCV antibodies should be followed by RNA testing to determine chronic hepatitis C[237,238].
- *Efforts to assure access to antiviral therapy for chronic hepatitis C*, such as government, industry, and payers agreements; training for primary care providers to effectively refer patients; etc[237,238] **(G0101)**.
- *Broad-based educational efforts* able to increase the understanding of the disease, which is still connected to stigma. These should aim patients and their family, as well as health care providers and the society as a whole.[239] Patients have also stated to need information about basic disease process, details of disease transmission, jargon clarification, and long-term medical issues resulting from HCV or HCV/HIV coinfection[240].
- *Considering the impact in patients' mental health*, before and during the treatment. A large number of patients undergoing treatment for HCV infection should be referred for psychiatric evaluation and, if necessary, should receive treatment for depression and other neuropsychiatric symptoms. Psychopathologic symptoms (depression, cognitive disorders) may be associated to HCV infection[239] **(A0005)**.

- *Maintaining HCV prevention actions* to avoid risky behaviours[237].

There is growing evidence that drug users can be treated when given adequate psycho-social support and community-based, low-barrier health care[241]. Even though reported experiences may not be generalizable to all drug users in all settings[238,242], several strategies for enhancing care programs for this population have been described:

- Effective management of complex barriers to care related to substance use, mental health, trauma, poverty, homelessness, criminalization, cultural issues, stigma, and marginalization[243].
- HCV treatment in low-threshold settings which are culturally appropriate and where trusting relationships between clients and providers are nurtured[243].
- Peer support programs, considering the importance of peers for getting HCV treatment knowledge[237,238].

A qualitative study conducted in Australia highlights gender-specific needs for HCV-infected women around diagnosis, reproductive health, and psycho-social wellbeing[244].

Another study[245] suggest actions for improving access to care for migrants which comprise community-specific awareness programmes and more culturally sensitive health services, including health professionals speaking other languages.

[H0006] How do patients, citizens and the important others using the technology react and act upon the technology?

No specific evidence is available at the moment on new DAAs, while many barriers emerged from literature on barriers posed by interferon therapy. In the latter case, patients reacted strongly to interferon's side effects[237], drug-drug interactions, and the risk of antiviral drug resistance. The high costs of DAAs could be a further barrier from patients' point of view.

Patients who were waiting, given their physician's decision, new and improved therapies **(A0011)** with new DAAs are likely to receive a treatment and in case of clinical success to be satisfied.

[H0011] What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?

Availability of new treatments, with high expectation of clinical success, give more importance to HCV screening **(H0003)**. A well planned HCV screening will required to identify people at risk and invest in viral testing technologies. The final aim is to interrupt HCV transmission[237].

A wider access to new DAAs would resolve the "warehousing" of patients phenomena **(A0011)**.

[H0009] What influences patients' or citizens' decisions to use the technology?

Qualitative and quantitative analysis have been performed to identify factors able to predict HCV treatment uptake[238-242,246] by different populations (drug users, marginalized population, etc.).

The major factors link to treatment uptake and adherence are:

- Benefit-risk profile of the drug. Patients' expectations on it play a crucial role. The actual benefit-risk profile should be communicated to patients to reach higher adherence. Patients should be aware of risks and potential impact on daily life to be motivated to respect posology.
- Concern about the overall safety profile of treatment (side effects, drug-to-drug interactions, etc.).
- Oral vs. intravenous treatment.
- Treatment schedule (frequency and duration).
- Impact on QoL as perceived by patients.
- Awareness of the disease (experiencing symptoms of HCV, impact on physical health, perceived seriousness, possible future health problems from not treating HCV, etc.).

- Patient's attitude (positive motivation to obtain HCV treatment, general desire to 'get well', life priorities, participant's willpower).
- Lack of barriers to engaging with HCV care **(H0003)**. A key role is played by presence of engaged clinicians, an accessible treatment pathway, availability of support, and ability to obtain information during treatment.
- Availability of HCV testing and HCV-related services at sites where providers have an understanding of addiction and are accustomed to and respectful of specific class of patients as drug users.
- Effective referral to specialists able to support patients **(H0003)**.
- Availability of supporting services to HCV patients with depression and other neuropsychiatric symptoms.
- Socio-economic status, as showed in the study of Charlebois et al. [241] for marginalized populations.

7.3. Discussion

Social impact of new DAAs diffusion is different for HCV sub-group of patients (drug-users, patients with mental disorders, marginalized populations). Ad hoc supporting services should be provided in order to reach a higher coverage and adherence to therapies **(H0003)**. To design support services attention should be paid to factors influencing patients' uptake and adherence to new therapies **(H0009)**.

HCV screening acquires more relevance given availability of more effective treatments **(H0011)**. At the same time, HCV prevention campaigns must be maintained in order to reduce and interrupt HCV transmission **(H0003)**.

The importance of addressing social determinants (such as stigma, discrimination, poverty, among others) as a part of HCV care programs is highlighted by many authors.

References

1. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013;368:34-44.
2. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211-21.
3. Micromedex Drugdex Database. Truven Health Analytics Inc., 2015.
4. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. N Engl J Med 2014;370:222-32.
5. Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013;368:45-53.
6. Lawitz E, Sullivan G, Rodriguez-Torres M, et al. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. J Infect 2015;70:197-205.
7. Hayashi N, Seto C, Kato M, et al. Once-daily simeprevir (TMC435) with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1-infected patients in Japan: the DRAGON study. J Gastroenterol 2014;49:138-47.
8. Izumi N, Hayashi N, Kumada H, et al. Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies. J Gastroenterol 2014;49:941-53.
9. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879-88.
10. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014;383:515-23.
11. Kumada H, Hayashi N, Izumi N, et al. Simeprevir (TMC435) once daily with peginterferon-alpha-2b and ribavirin in patients with genotype 1 hepatitis C virus infection: The CONCERTO-4 study. Hepatol Res 2015;45:501-13.
12. Hayashi N, Izumi N, Kumada H, et al. Simeprevir with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial. J Hepatol 2014;61:219-27.
13. CADTH. Direct-Acting Antiviral Agents for Chronic Hepatitis C Genotype 1. 2014. [Cited October 2015] https://www.cadth.ca/sites/default/files/pdf/TR0007_HepC_ScienceReport_e.pdf.
14. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. 2011. [Cited October 2015] http://handbook.cochrane.org/.
15. European Network for Health Technology Assessment (EUnetHTA). Level of evidence. Internal validity of randomized controlled trials. 2013. [Cited October 2015] http://www.eunethta.eu/eunethta-guidelines.
16. EMA. Sovaldi (sofosbuvir). Summary of Product Characteristics. 2015;
17. EMA. Harvoni (ledipasvir+ sofosbuvir). Summary of Product Characteristics. 2015;
18. EMA. Olysio (simeprevir). Summary of Product Characteristics. 2015;
19. EMA. Daklinza (daclatasvir). Summary of Product Characteristics. 2015;
20. EMA. Viekirax (ombitasvir+paritaprevir+ ritonavir). Summary of Product Characteristics. 2015;
21. EMA. Exviera (dasabuvir). Summary of Product Characteristics. 2015;
22. FDA. Drugs. 2015. [Cited October 2015] http://www.fda.gov/Drugs/default.htm.
23. EMA. Pegasys (peginterferon alfa-2a). Summary of Product Characteristics. 2014;
24. EMA. PegIntron (peginterferon alfa-2b). Summary of Product Characteristics. 2014;
25. EMA. Ribavirin Teva Pharma B.V. (ribavirin). Summary of Product Characteristics. 2014;
26. EMA. Incivo (telaprevir). Summary of Product Characteristics. 2015;
27. EMA. Victrelis (boceprevir). Summary of Product Characteristics. 2015;
28. EMA recommends avoidance of certain hepatitis C medicines and amiodarone together. 2015. [Cited November 2015] http://tinyurl.com/grb2xsh.
29. FDA. Serious Symptomatic Bradycardia When Co-administered with Sofosbuvir and Amiodarone. 2015. [Cited November 2015] http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm417602.htm.
30. FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie . 2015. [Cited November 2015] http://www.fda.gov/downloads/Drugs/DrugSafety/UCM468755.pdf.
31. EMA. ViraferonPeg (peginterferon alfa-2a). Summary of Product Characteristics. 2015;
32. EMA. Ribavirin Mylan (ribavirin). Summary of Product Characteristics. 2015;
33. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015;62:932-54.

34. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015;63:199-236.
35. Horner SM, Naggie S. Successes and Challenges on the Road to Cure Hepatitis C. PLoS Pathog 2015;11:e1004854.
36. Ippolito G, Capobianchi MR, Lanini S, et al. Is hepatitis C virus eradication around the corner only 25 years after its discovery? Int J Antimicrob Agents 2015;45:111-2.
37. Jayasekera CR, Barry M, Roberts LR, et al. Treating hepatitis C in lower-income countries. N Engl J Med 2014;370:1869-71.
38. WHO. Guidelines for the screening, care and treatment of persons with hepatitis infection. 2014. [Cited September 2015] http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf.
39. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359-62.
40. Lee MH, Yang HI, Yuan Y, et al. Epidemiology and natural history of hepatitis C virus infection. World J Gastroenterol 2014;20:9270-80.
41. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Pract Res Clin Gastroenterol 2012;26:401-12.
42. Mosley JW, Operskalski EA, Tobler LH, et al. Viral and host factors in early hepatitis C virus infection. Hepatology 2005;42:86-92.
43. Zein NN. Clinical significance of hepatitis C virus genotypes. Clin Microbiol Rev 2000;13:223-35.
44. Simmonds P, Alberti A, Alter HJ, et al. A proposed system for the nomenclature of hepatitis C viral genotypes. Hepatology 1994;19:1321-4.
45. Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology 2014;59:318-27.
46. Commission Decision 2008/426/EC of 28 April 2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Official Journal of the European Union; L159, 2008. [Cited September 2015] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:159:0046:0090:EN:PDF.
47. Duffell EF, van de Laar MJW, Amato-Gauci AJ. Enhanced surveillance of hepatitis C in the EU, 2. J Viral Hepat 2015;22:590-5.
48. Duffell EF, van de Laar MJW, Amato-Gauci AJ. Enhanced surveillance of hepatitis B in the EU, 2006-2012. J Viral Hepat 2015;22:581-9.
49. Hatzakis A, Chulanov V, Gadano AC, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm - volume 2. J Viral Hepat 2015;22 Suppl 1:26-45.
50. Saraswat V, Norris S, de Knegt RJ, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 2. J Viral Hepat 2015;22 Suppl 1:6-25.
51. Wedemeyer H, Dore GJ, Ward JW. Estimates on HCV disease burden worldwide - filling the gaps. J Viral Hepat 2015;22 Suppl 1:1-5.
52. Gane E, Kershenobich D, Seguin-Devaux C, et al. Strategies to manage hepatitis C virus (HCV) infection disease burden - volume 2. J Viral Hepat 2015;22 Suppl 1:46-73.
53. Mühlberger N, Schwarzer R, Lettmeier B, et al. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. BMC Public Health 2009;9:34.
54. Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect 2011;17:107-15.
55. European Centre for Disease Prevention and Control (ECDC). Surveillance and prevention of hepatitis B and C in Europe. 2010. [Cited September 2015] http://ecdc.europa.eu/en/publications/Publications/101012_TER_HepBandC_survey.pdf.
56. Blachier M, Leleu H, Peck-Radosavljevic M, et al. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013;58:593-608.
57. Mohd Hanafiah K, Groeger J, Flaxman AD, et al. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013;57:1333-42.
58. Cornberg M, Razavi HA, Alberti A, et al. A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel. Liver Int 2011;31 Suppl 2:30-60.
59. European Centre for Disease Prevention and Control (ECDC). Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies. 2010. [Cited September 2015]

http://ecdc.europa.eu/en/publications/Publications/TER_100914_Hep_B_C%20_EU_neighbourhood.pdf.
60. Bruggmann P, Berg T, Ovrehus ALH, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat 2014;21 Suppl 1:5-33.
61. Mathurin P. HCV burden in Europe and the possible impact of current treatment. Dig Liver Dis 2013;45 Suppl 5:S314-S317.
62. Roy K, Hay G, Andragetti R, et al. Monitoring hepatitis C virus infection among injecting drug users in the European Union: a review of the literature. Epidemiol Infect 2002;129:577-85.
63. Rafiq SM, Rafiq SM, Banik GR, et al. Current Burden of Hepatitis C Virus Infection among Injecting Drug Users: A Mini Systematic Review of Prevalence Studies. Infect Disord Drug Targets 2014;aheadofprint Oct 14.
64. van de Laar TJW, van der Bij AK, Prins M, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007;196:230-8.
65. Cavlek TV, Margan IG, Lepej SZ, et al. Seroprevalence, risk factors, and hepatitis C virus genotypes in groups with high-risk sexual behavior in Croatia. J Med Virol 2009;81:1348-53.
66. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 2006;3:47-52.
67. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-72.
68. Planas R, Balleste B, Alvarez MA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol 2004;40:823-30.
69. Bosetti C, Levi F, Boffetta P, et al. Trends in mortality from hepatocellular carcinoma in Europe, 1980-2004. Hepatology 2008;48:137-45.
70. Bosetti C, Levi F, Lucchini F, et al. Worldwide mortality from cirrhosis: an update to 2002. J Hepatol 2007;46:827-39.
71. La Vecchia C, Lucchini F, Franceschi S, et al. Trends in mortality from primary liver cancer in Europe. Eur J Cancer 2000;36:909-15.
72. Aspinall EJ, Hutchinson SJ, Janjua NZ, et al. Trends in mortality after diagnosis of hepatitis C virus infection: an international comparison and implications for monitoring the population impact of treatment. J Hepatol 2015;62:269-77.
73. Deuffic-Burban S, Deltenre P, Buti M, et al. Predicted effects of treatment for HCV infection vary among European countries. Gastroenterology 2012;143:974-85.
74. Public Health England. Hepatitis C in the UK. 2014. [Cited September 2015] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/337115/HCV_in_the_UK_2014_24_July.pdf.
75. Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol 2008;48:148-62.
76. Negro F. Epidemiology of hepatitis C in Europe. Dig Liver Dis 2014;46 Suppl 5:S158-S164.
77. Wandeler G, Gsponer T, Bregenzer A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clin Infect Dis 2012;55:1408-16.
78. Wandeler G, Schlauri M, Jaquier ME, et al. Incident Hepatitis C Virus Infections in the Swiss HIV Cohort Study: Changes in Treatment Uptake and Outcomes Between 1991 and 2013. Open Forum Infect Dis 2015;2:ofv026.
79. Bellentani S, Pozzato G, Saccoccio G, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. Gut 1999;44:874-80.
80. Bellentani S, Tiribelli C. The spectrum of liver disease in the general population: lesson from the Dionysos study. J Hepatol 2001;35:531-7.
81. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825-32.
82. Abdel-Hady M, Bunn SK, Sira J, et al. Chronic hepatitis C in children--review of natural history at a National Centre. J Viral Hepat 2011;18:e535-e540.
83. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264-73.
84. McDonald SA, Hutchinson SJ, Bird SM, et al. Hospitalization of hepatitis C-diagnosed individuals in Scotland for decompensated cirrhosis: a population-based record-linkage study. Eur J Gastroenterol Hepatol 2010;22:49-57.

85. McCombs J, Matsuda T, Tonnu-Mihara I, et al. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. JAMA Intern Med 2014;174:204-12.
86. Kumar V, Kato N, Urabe Y, et al. Genome-wide association study identifies a susceptibility locus for HCV-induced hepatocellular carcinoma. Nat Genet 2011;43:455-8.
87. Donato F, Tagger A, Gelatti U, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002;155:323-31.
88. Raimondi S, Bruno S, Mondelli MU, et al. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. J Hepatol 2009;50:1142-54.
89. Bertoletti A, Ferrari C. Kinetics of the immune response during HBV and HCV infection. Hepatology 2003;38:4-13.
90. Farci P, Alter HJ, Wong D, et al. A long-term study of hepatitis C virus replication in non-A, non-B hepatitis. N Engl J Med 1991;325:98-104.
91. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. Hepatology 1997;26:15S-20S.
92. Thimme R, Oldach D, Chang KM, et al. Determinants of viral clearance and persistence during acute hepatitis C virus infection. J Exp Med 2001;194:1395-406.
93. Cox AL, Netski DM, Mosbruger T, et al. Prospective evaluation of community-acquired acute-phase hepatitis C virus infection. Clin Infect Dis 2005;40:951-8.
94. Grebely J, Prins M, Hellard M, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. Lancet Infect Dis 2012;12:408-14.
95. Farci P, Alter HJ, Shimoda A, et al. Hepatitis C virus-associated fulminant hepatic failure. N Engl J Med 1996;335:631-4.
96. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.
97. National Institutes of Health. Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002. Hepatology 2002;36:S3-20.
98. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002;36:S35-S46.
99. Forns X, Ampurdanes S, Sanchez-Tapias JM, et al. Long-term follow-up of chronic hepatitis C in patients diagnosed at a tertiary-care center. J Hepatol 2001;35:265-71.
100. Wiese M, Berr F, Lafrenz M, et al. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. Hepatology 2000;32:91-6.
101. Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology 1996;23:1334-40.
102. Anthony PP, Ishak KG, Nayak NC, et al. The morphology of cirrhosis. Recommendations on definition, nomenclature, and classification by a working group sponsored by the World Health Organization. J Clin Pathol 1978;31:395-414.
103. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335-74.
104. Amin J, Dore GJ, O'Connell DL, et al. Cancer incidence in people with hepatitis B or C infection: a large community-based linkage study. J Hepatol 2006;45:197-203.
105. Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology 2006;43:1303-10.
106. Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum 1999;42:2204-12.
107. Zignego AL, Ferri C, Pileri SA, et al. Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical approach. Dig Liver Dis 2007;39:2-17.
108. Duberg AS, Nordstrom M, Torner A, et al. Non-Hodgkin's lymphoma and other nonhepatic malignancies in Swedish patients with hepatitis C virus infection. Hepatology 2005;41:652-9.
109. Amin J, Law MG, Bartlett M, et al. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet 2006;368:938-45.
110. Allison RD, Tong X, Moorman AC, et al. Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006-2010. J Hepatol 2015;63:822-8.
111. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677-84.
112. Pham TNQ, MacParland SA, Mulrooney PM, et al. Hepatitis C virus persistence after spontaneous or treatment-induced resolution of hepatitis C. J Virol 2004;78:5867-74.
113. Attar BM, Van Thiel D. A New Twist to a Chronic HCV Infection: Occult Hepatitis C. Gastroenterol Res Pract 2015;2015:579147.

114. Keyvani H, Bokharaei-Salim F, Monavari SH, et al. Occult hepatitis C virus infection in candidates for liver transplant with cryptogenic cirrhosis. Hepat Mon 2013;13:e11290.
115. Castillo I, Pardo M, Bartolome J, et al. Occult hepatitis C virus infection in patients in whom the etiology of persistently abnormal results of liver-function tests is unknown. J Infect Dis 2004;189:7-14.
116. Whiteley D, Elliott L, Cunningham-Burley S, et al. Health-Related Quality of Life for individuals with hepatitis C: A narrative review. Int J Drug Policy 2015;26:936-49.
117. Tong MJ, el-Farra NS, Reikes AR, et al. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995;332:1463-6.
118. Rieu V, Cohen P, Andre MH, et al. Characteristics and outcome of 49 patients with symptomatic cryoglobulinaemia. Rheumatology (Oxford) 2002;41:290-300.
119. Ferri C. Mixed cryoglobulinemia. Orphanet J Rare Dis 2008;3:25.
120. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. J Hepatol 2008;49:831-44.
121. Weissenborn K, Krause J, Bokemeyer M, et al. Hepatitis C virus infection affects the brain-evidence from psychometric studies and magnetic resonance spectroscopy. J Hepatol 2004;41:845-51.
122. Gidding HF, Amin J, Dore GJ, et al. Hospital-related morbidity in people notified with hepatitis C: a population-based record linkage study in New South Wales, Australia. J Hepatol 2010;53:43-9.
123. Rosenberg DM, Cook SF, Lanza LL. Health care, treatment patterns and cost of services for patients infected with chronic hepatitis C virus in a large insured New England population. J Viral Hepat 2000;7:361-7.
124. Grant WC, Jhaveri RR, McHutchison JG, et al. Trends in health care resource use for hepatitis C virus infection in the United States. Hepatology 2005;42:1406-13.
125. Myers RP, Liu M, Shaheen AA. The burden of hepatitis C virus infection is growing: a Canadian population-based study of hospitalizations from 1994 to 2004. Can J Gastroenterol 2008;22:381-7.
126. Thomson SJ, Westlake S, Rahman TM, et al. Chronic liver disease--an increasing problem: a study of hospital admission and mortality rates in England, 1979-2005, with particular reference to alcoholic liver disease. Alcohol Alcohol 2008;43:416-22.
127. Marcellusi A, Viti R, Capone A, et al. The economic burden of HCV-induced diseases in Italy. A probabilistic cost of illness model. Eur Rev Med Pharmacol Sci 2015;19:1610-20.
128. Mennini FS, Marcellusi A, Andreoni M, et al. Health policy model: long-term predictive results associated with the management of hepatitis C virus-induced diseases in Italy. Clinicoecon Outcomes Res 2014;6:303-10.
129. Nevens F, Colle I, Michielsen P, et al. Resource use and cost of hepatitis C-related care. Eur J Gastroenterol Hepatol 2012;24:1191-8.
130. Stahmeyer JT, Rossol S, Bert F, et al. Cost of treating hepatitis C in Germany: a retrospective multicenter analysis. Eur J Gastroenterol Hepatol 2014;26:1278-85.
131. Müllhaupt B, Bruggmann P, Bihl F, et al. Modeling the Health and Economic Burden of Hepatitis C Virus in Switzerland. PLoS One 2015;10:e0125214.
132. Starkel P, Vandijck D, Laleman W, et al. The disease burden of hepatitis C in Belgium: development of a realistic disease control strategy. Acta Gastroenterol Belg 2014;77:280-4.
133. Vandijck D, Moreno C, Starkel P, et al. Current and future health and economic impact of hepatitis C in Belgium. Acta Gastroenterol Belg 2014;77:285-90.
134. Starkel P, Vandijck D, Laleman W, et al. The Disease Burden of Hepatitis C in Belgium : An update of a realistic disease control strategy. Acta Gastroenterol Belg 2015;78:228-32.
135. European Liver Patients Association (ELPA). Burden of hepatitis C in Europe - the case of France and Romania. 2015. [Cited September 2015] http://www.elpa-info.org/tl_files/elpa_news/elpa/2015/Burden-of-Hepatitis-C.pdf .
136. Umar M, Khan AG, Abbas Z, et al. World Gastroenterology Organisation global guidelines: diagnosis, management and prevention of hepatitis C April 2013. J Clin Gastroenterol 2014;48:204-17.
137. Myers RP, Shah H, Burak KW, et al. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol 2015;29:19-34.
138. Lettmeier B, Muhlberger N, Schwarzer R, et al. Market uptake of new antiviral drugs for the treatment of hepatitis C. J Hepatol 2008;49:528-36.

139. Brennan T, Shrank W. New expensive treatments for hepatitis C infection. JAMA 2014;312:593-4.
140. Ministerio de Sanidad Servicios Sociales e Igualdad. Más de 18.000 pacientes han recibido en el primer semestre de 2015 tratamientos de Hepatitis C de última generación en España. Notas de prensa. 2015. [Cited June 2015] http://www.msssi.gob.es/gabinete/notasPrensa.do?id=3734 .
141. Younossi Z, Henry L. Systematic review: patient-reported outcomes in chronic hepatitis C--the impact of liver disease and new treatment regimens. Aliment Pharmacol Ther 2015;41:497-520.
142. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-98.
143. Mizokami M, Yokosuka O, Takehara T, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis 2015;15:645-53.
144. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973-82.
145. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604-14.
146. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-93.
147. Osinusi A, Kohli A, Marti MM, et al. Re-treatment of chronic hepatitis C virus genotype 1 infection after relapse: an open-label pilot study. Ann Intern Med 2014;161:634-8.
148. Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis 2015;15:397-404.
149. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594-603.
150. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983-92.
151. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014;384:1756-65.
152. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359-65.
153. Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's class A cirrhosis. Gastroenterology 2015;148:762-70.
154. Foster GR, Foster GR, Pianko S, et al. Efficacy of Sofosbuvir Plus Ribavirin With or Without Peginterferon-Alfa in Patients With Hepatitis C Virus Genotype 3 Infection and Treatment-Experienced Patients With Cirrhosis and Hepatitis C Virus Genotype 2 Infection. Gastroenterology 2015;aheadofprint Aug 4.
155. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368:1867-77.
156. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.
157. Omata M, Nishiguchi S, Ueno Y, et al. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. J Viral Hepat 2014;21:762-8.
158. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993-2001.
159. Nelson D, Cooper J, Lalezari J, et al. All oral 12 week treatment with daclatasvir plus sofosbuvir in patients with chronic hepatitis C virus genotype 3 infection ally 3 phase 3 study. Hepatol Int 2015;9:S56.
160. Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis 2015;15:1049-54.
161. Ruane PJ, Ain D, Stryker R, et al. Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry. J Hepatol 2015;62:1040-6.

162. Reddy KR, Zeuzem S, Zoulim F, et al. Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): a randomised, double-blind, non-inferiority phase 3 trial. Lancet Infect Dis 2015;15:27-35.
163. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. Hepatology 2015;61:769-75.
164. Dore GJ, Lawitz E, Hezode C, et al. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. Gastroenterology 2015;148:355-66.
165. Hezode C, Hirschfield GM, Ghesquiere W, et al. Daclatasvir plus peginterferon alfa and ribavirin for treatment-naive chronic hepatitis C genotype 1 or 4 infection: a randomised study. Gut 2015;64:948-56.
166. Moreno C, Hezode C, Marcellin P, et al. Efficacy and safety of simeprevir with PegIFN/ribavirin in naive or experienced patients infected with chronic HCV genotype 4. J Hepatol 2015;62:1047-55.
167. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet 2013;381:2100-7.
168. Dieterich D, Rockstroh JK, Orkin C, et al. Simeprevir (TMC435) with pegylated interferon/ribavirin in patients coinfected with HCV genotype 1 and HIV-1: a phase 3 study. Clin Infect Dis 2014;59:1579-87.
169. Molina JM, Orkin C, Iser DM, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. Lancet 2015;385:1098-106.
170. Naggie S, Cooper C, Saag M, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med 2015;373:705-13.
171. Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. JAMA 2015;313:1232-9.
172. Rodriguez-Torres M, Gaggar A, Shen G, et al. Sofosbuvir for chronic hepatitis C virus infection genotype 1-4 in patients coinfected with HIV. J Acquir Immune Defic Syndr 2015;68:543-9.
173. Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA 2014;312:353-61.
174. Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. JAMA 2015;313:1223-31.
175. Wyles DL, Ruane PJ, Sulkowski MS, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med 2015;373:714-25.
176. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology 2015;149:649-59.
177. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med 2014;371:2375-82.
178. Punzalan CS, Punzalan CS, Barry C, et al. Sofosbuvir plus Simeprevir Treatment of Recurrent Genotype 1 Hepatitis C after Liver Transplant. Clin Transplant 2015;aheadofprint Sep 11.
179. Pungpapong S, Aqel B, Leise M, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. Hepatology 2015;61:1880-6.
180. Charlton M, Gane E, Manns MP, et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology 2015;148:108-17.
181. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015;148:100-7.
182. Lalezari J, Sullivan JG, Varunok P, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol 2015;63:364-9.
183. Younossi ZM, Stepanova M, Henry L, et al. Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). J Hepatol 2014;60:741-7.
184. Younossi ZM, Stepanova M, Zeuzem S, et al. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: the VALENCE study. J Hepatol 2014;61:228-34.

185. Younossi ZM, Stepanova M, Nader F, et al. Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens. Hepatology 2014;59:2161-9.
186. Younossi ZM, Stepanova M, Sulkowski M, et al. Sofosbuvir and Ribavirin for Treatment of Chronic Hepatitis C in Patients Coinfected With Hepatitis C Virus and HIV: The Impact on Patient-Reported Outcomes. J Infect Dis 2015;212:367-77.
187. Younossi ZM, Stepanova M, Marcellin P, et al. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: Results from the ION-1, -2, and -3 clinical trials. Hepatology 2015;61:1798-808.
188. Lundh A, Sismondo S, Lexchin J, et al. Industry sponsorship and research outcome. Cochrane Database Syst Rev 2012;12:MR000033.
189. Veldt BJ, Saracco G, Boyer N, et al. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. Gut 2004;53:1504-8.
190. Yoshida EM, Sulkowski MS, Gane EJ, et al. The Concordance between SVR4, SVR12, and SVR24 in patients with chronic HCV infection who received treatment with sofosbuvir in phase 3 clinical trials. Hepatology 2013;58:734A.
191. Holmberg SD, Spradling PR, Moorman AC, et al. Hepatitis C in the United States. N Engl J Med 2013;368:1859-61.
192. Koretz RL, Pleguezuelo M, Arvaniti V, et al. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. Cochrane Database Syst Rev 2013;1:CD003617.
193. Hauser G, Awad T, Brok J, et al. Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C. Cochrane Database Syst Rev 2014;2:CD005441.
194. Morisco F, Granata R, Stroffolini T, et al. Sustained virological response: a milestone in the treatment of chronic hepatitis C. World J Gastroenterol 2013;19:2793-8.
195. van der Meer AJ. Achieving sustained virological response: what's the impact on further hepatitis C virus-related disease? Expert Rev Gastroenterol Hepatol 2015;9:559-66.
196. Mallat A, Hezode C, Lotersztajn S. Environmental factors as disease accelerators during chronic hepatitis C. J Hepatol 2008;48:657-65.
197. Butt AA, Yan P, Lo Re V, et al. Liver fibrosis progression in hepatitis C virus infection after seroconversion. JAMA Intern Med 2015;175:178-85.
198. European Network for Health Technology Assessment (EUnetHTA). HTA Core Model Handbook Online, Version1.5. 2014. [Cited October 2015] http://meka.thl.fi/htacore/ViewHandbook.aspx.
199. European Network for Health Technology Assessment (EUnetHTA). HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals, Version3.0. 2013. [Cited October 2015] https://eunethta.fedimbo.belgium.be/.
200. Whitlock EP, Lin JS, Chou R, et al. Using existing systematic reviews in complex systematic reviews. Ann Intern Med 2008;148:776-82.
201. Robinson KA, Whitlock EP, O'Neil ME, Anderson JK, Hartling L, Dryden DM, et al. Integration of Existing Systematic Reviews. Rockville (MD): 2014. [Cited October 2015] http://www.ncbi.nlm.nih.gov/books/NBK216379/.
202. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA 2013;310:804-11.
203. Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology 2014;146:736-43.
204. Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet 2015;385:2502-9.
205. Stedman CAM, Stedman CA, Hyland RH, et al. Once daily ledipasvir/sofosbuvir fixed-dose combination with ribavirin in patients with inherited bleeding disorders and hepatitis C genotype 1 infection. Haemophilia 2015;aheadofprint Aug 28.
206. Modi AA, Modi AA, Nazario H, et al. Safety and efficacy of Simeprevirplus Sofosbuvir with or without Ribavirin in patients with decompensated genotype 1 hepatitis C cirrhosis. Liver Transpl 2015;aheadofprint Sep 3.
207. California Technology Assessment Forum. The Comparative Clinical Effectiveness and Value of Novel Combination Therapies for the Treatment of Patients with Genotype 1 Chronic Hepatitis C Infection. 2015. [Cited October 2015] http://ctaf.org/sites/default/files/assessments/CTAF_HCV2_Final_Report_013015.pdf.
208. Burgess S, Partovi N, Yoshida EM, et al. Drug Interactions With Direct-Acting Antivirals for Hepatitis C: Implications for HIV and Transplant Patients. Ann Pharmacother 2015;49:674-87.

209. Fazel Y, Lam B, Golabi P, et al. Safety analysis of sofosbuvir and ledipasvir for treating hepatitis C. Expert Opin Drug Saf 2015;14:1317-26.
210. Kwo PY, Badshah MB. New hepatitis C virus therapies: drug classes and metabolism, drug interactions relevant in the transplant settings, drug options in decompensated cirrhosis, and drug options in end-stage renal disease. Curr Opin Organ Transplant 2015;20:235-41.
211. Cholongitas E, Pipili C, Papatheodoridis G. Interferon-free regimens for the treatment of hepatitis C virus in liver transplant candidates or recipients. World J Gastroenterol 2015;21:9526-33.
212. National Institute of Health. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2010. [Cited October 2015] http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
213. European Network for Health Technology Assessment (EUnetHTA). Endpoints used for relative effectiveness assessment of pharmaceuticals: Safety. 2013. [Cited October 2015] http://www.eunethta.eu/eunethta-guidelines.
214. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. BMJ Open 2013;3:e002496.
215. Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. PLoS Med 2012;9:e1001201.
216. Eichler HG, Abadie E, Breckenridge A, et al. Open clinical trial data for all? A view from regulators. PLoS Med 2012;9:e1001202.
217. Wieseler B, Kerekes MF, Vervoelgyi V, et al. Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications. BMJ 2012;344:d8141.
218. Lazarus JV, Lundgren J, Casabona J, et al. Roundtable discussion: how lessons learned from HIV can inform the global response to viral hepatitis. BMC Infect Dis 2014;14 Suppl 6:S18.
219. European Monitoring Centre for Drugs and Drug Addiction. Perspectives on Drugs: hepatitis C treatment for injecting drug users. 2015. [Cited October 2015] http://www.emcdda.europa.eu/topics/pods/hepatitis-c-treatment .
220. Martin NK, Vickerman P, Foster GR, et al. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol 2011;54:1137-44.
221. Maticic M, Videcnik Zorman J, Gregorcic S, et al. Are there national strategies, plans and guidelines for the treatment of hepatitis C in people who inject drugs? A survey of 33 European countries. BMC Infect Dis 2014;14 Suppl 6:S14.
222. Arain A, Robaeys G, Stover H. Hepatitis C in European prisons: a call for an evidence-informed response. BMC Infect Dis 2014;14 Suppl 6:S17.
223. Linas BP, Barter DM, Leff JA, et al. The hepatitis C cascade of care: identifying priorities to improve clinical outcomes. PLoS One 2014;9:e97317.
224. Harris M, Rhodes T. Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors. Harm Reduct J 2013;10:7.
225. Aronsohn A, Jensen D. Informed deferral: a moral requirement for entry into the hepatitis C virus treatment warehouse. Hepatology 2012;56:1591-2.
226. Simon TG, Simon TG, Chung RT, et al. HEP-15-1079: The new HCV bottleneck: can delaying therapy be justified Reply to Letter to the Editor (LTE). Hepatology 2015;aheadofprint Aug 27.
227. Poynard T, Ratziu V, Charlotte F, et al. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol 2001;34:730-9.
228. AVERT. Antiretroviral Drug Prices. 2015. [Cited October 2015] http://www.avert.org/antiretroviral-drug-prices.htm.
229. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013. [Cited October 2015] http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1.
230. Beyrer C, Birx DL, Bekker LG, et al. The Vancouver Consensus: antiretroviral medicines, medical evidence, and political will. Lancet 2015;386:505-7.
231. Hatzakis A, Wait S, Bruix J, et al. The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference*. J Viral Hepat 2011;18 Suppl 1:1-16.
232. Sacchini D, Craxi L, Refolo P, et al. Ethical assessment of hepatitis C virus treatment: The lesson from first generation protease inhibitors. Dig Liver Dis 2015;47:351-5.
233. Deuffic-Burban S, Mathurin P, Rosa I, et al. Impact of emerging hepatitis C virus treatments on future needs for liver transplantation in France: a modelling approach. Dig Liver Dis 2014;46:157-63.

234. Papatheodoridis GV, Tsochatzis E, Hardtke S, et al. Barriers to care and treatment for patients with chronic viral hepatitis in Europe: a systematic review. Liver Int 2014;34:1452-63.
235. Ministerio de Sanidad Servicios Sociales e Igualdad de España. Plan estratégico para el abordaje de la Hepatitis C en el Sistema Nacional de Salud. 2015. [Cited September 2015] http://www.msssi.gob.es/ciudadanos/enfLesiones/enfTransmisibles/docs/plan_estrategico_hepatitis_C.pdf.
236. Mitruka K, Tsertsvadze T, Butsashvili M, et al. Launch of a Nationwide Hepatitis C Elimination Program - Georgia, April 2015. MMWR Morb Mortal Wkly Rep 2015;64:753-7.
237. Edlin BR, Winkelstein ER. Can hepatitis C be eradicated in the United States? Antiviral Res 2014;110:79-93.
238. Jordan AE, Masson CL, Mateu-Gelabert P, et al. Perceptions of drug users regarding hepatitis C screening and care: a qualitative study. Harm Reduct J 2013;10:10.
239. Marinho RT, Barreira DP. Hepatitis C, stigma and cure. World J Gastroenterol 2013;19:6703-9.
240. North CS, Devereaux R, Pollio DE, et al. Patient perspectives on hepatitis C and its treatment. Eur J Gastroenterol Hepatol 2014;26:74-81.
241. Charlebois A, Lee L, Cooper E, et al. Factors associated with HCV antiviral treatment uptake among participants of a community-based HCV programme for marginalized patients. J Viral Hepat 2012;19:836-42.
242. Treloar C, Rance J, Dore GJ, et al. Barriers and facilitators for assessment and treatment of hepatitis C virus infection in the opioid substitution treatment setting: insights from the ETHOS study. J Viral Hepat 2014;21:560-7.
243. Milne R, Price M, Wallace B, et al. From principles to practice: Description of a novel equity-based HCV primary care treatment model for PWID. Int J Drug Policy 2015;26:1020-7.
244. Olsen A, Temple-Smith M, Banwell C. Consideration of gender in diagnosis and management of blood-borne viruses: the case of hepatitis C. Aust J Prim Health 2013;19:124-9.
245. Guirgis M, Nusair F, Bu YM, et al. Barriers faced by migrants in accessing healthcare for viral hepatitis infection. Intern Med J 2012;42:491-6.
246. Fusfeld L, Aggarwal J, Dougher C, et al. Assessment of motivating factors associated with the initiation and completion of treatment for chronic hepatitis C virus (HCV) infection. BMC Infect Dis 2013;13:234.

