NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ledipasvir–sofosbuvir for treating chronic hepatitis C

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ledipasvir–sofosbuvir in the NHS in England. The Appraisal Committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, and clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the Committee papers).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ledipasvir–sofosbuvir in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: Monday 23 March 2015

Second Appraisal Committee meeting: Wednesday 1 April

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Ledipasvir–sofosbuvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1.

Table 1 Ledipasvir–sofosbuvir for treating adults with chronic hepatitis C

<table>
<tr><th rowspan="2">Genotype*</th><th colspan="2">Ledipasvir–sofosbuvir</th><th colspan="2">Ledipasvir–sofosbuvir in combination with ribavirin</th></tr>
<tr><th>Treatment history</th><th>Recommendation</th><th>Treatment history</th><th>Recommendation</th></tr>
<tr><td rowspan="4">Adults with genotype 1 HCV</td><td rowspan="2">Treatment-naive</td><td>8 weeks' treatment recommended for people without cirrhosis;
12 weeks' treatment not recommended for people without cirrhosis</td><td rowspan="4">All</td><td rowspan="4">Not licensed for this population</td></tr>
<tr><td>12 weeks' treatment recommended for people with cirrhosis;
24 weeks' treatment not recommended for people with cirrhosis</td></tr>
<tr><td rowspan="2">Treatment-experienced</td><td>12 weeks' treatment recommended for people without cirrhosis;
24 weeks' treatment not recommended for people without cirrhosis</td></tr>
<tr><td>24 weeks' treatment not recommended for people with cirrhosis</td></tr>
<tr><td>Adults with genotype 3 HCV</td><td>All</td><td>Not licensed for this population</td><td>All</td><td>Not recommended</td></tr>
</table>

Adults with genotype 4 HCV	Treatment-naive	12 weeks' treatment not recommended for people without cirrhosis	All	Not licensed for this population
		12 weeks' treatment recommended for people with cirrhosis; 24 weeks' treatment not recommended for people with cirrhosis		
	Treatment-experienced	**12 weeks' treatment recommended for people without cirrhosis**; 24 weeks' treatment not recommended for people without cirrhosis		
		24 weeks' treatment not recommended for people with cirrhosis		
HCV, hepatitis C virus Treatment-naive – the person has not had treatment for chronic hepatitis C Treatment-experienced – the person's hepatitis C has not adequately responded to interferon-based treatment				

1.2 People whose treatment with ledipasvir–sofosbuvir is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Ledipasvir–sofosbuvir prevents hepatitis C virus (HCV) replication by inhibiting the NS5A (targeted by ledipasvir) and NS5B (targeted by sofosbuvir) proteins. Ledipasvir–sofosbuvir (Harvoni, Gilead Sciences) has a marketing authorisation in the UK for treating chronic hepatitis C in adults. However, the marketing authorisation recommends specific treatment durations for HCV genotypes 1, 3 and 4 only, and states that ledipasvir–sofosbuvir should not be used in people with HCV genotypes 2, 5 and 6. The recommended

dose is 1 daily tablet containing a fixed-dose combination of 90 mg ledipasvir and 400 mg sofosbuvir. It is taken orally for 8, 12 or 24 weeks, with or without ribavirin. The recommended treatment duration and whether ribavirin is co-administered depends on genotype, treatment history and presence of cirrhosis. For full details of the recommended treatment durations with or without ribavirin, see table 1 of the summary of product characteristics.

2.2 The summary of product characteristics lists the following 'very common' adverse reactions for ledipasvir–sofosbuvir, with or without ribavirin: fatigue and headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The cost of ledipasvir–sofosbuvir is £12,993.33 per 28 tablet pack (excluding VAT; company's evidence submission). The cost of a 12 week course of treatment is £38,979.99 and a 24 week course is £77,959.98 (both excluding VAT), not including the cost for ribavirin. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 8) considered evidence submitted by Gilead Sciences and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The company conducted a systematic literature review to identify studies evaluating the clinical effectiveness of ledipasvir–sofosbuvir for treating chronic hepatitis C. It presented 10 studies of ledipasvir–sofosbuvir with and without ribavirin in adults whose chronic hepatitis C was either previously untreated (described as treatment naive) or previously treated (described as treatment

experienced). The company focused its clinical-effectiveness submission on 3 phase III non-randomised controlled trials in people with HCV genotype 1 (ION-1 [treatment naive], ION-2 [treatment experienced] and ION-3 [treatment naive]). The other 7 studies submitted by the company were phase II studies and were included as 'supportive evidence'. Of these 7 studies:

- 2 included people with either treatment-naive or treatment-experienced genotype 1 HCV (ELECTRON, LONESTAR)
- 1 included people with treatment-experienced genotype 1 HCV (SIRIUS)
- 1 included people with either treatment-naive or treatment-experienced genotype 1 or 3 HCV (ELECTRON-2)
- 1 included people with either treatment-naive or treatment-experienced genotype 1 or 4 HCV (SYNERGY)
- 1 included people with genotype 1 HCV co-infected with HIV (ERADICATE)
- 1 included people with genotype 1 or 4 HCV with advanced liver disease or after liver transplant (SOLAR-1).

Only the results of studies of durations of ledipasvir–sofosbuvir treatment (with or without ribavirin) that have a marketing authorisation in the UK, and the results of studies included in the company's economic model, are presented here.

Genotype 1: Treatment-naive HCV

3.2 ION-1 was an international (99 centres in Europe and the USA; including 7 centres in England), open-label, non-randomised controlled trial of 865 adults with treatment-naive genotype 1 HCV. The treatment groups that supported the dosage in the UK marketing authorisation were:

- ledipasvir–sofosbuvir once daily for 12 weeks (n=214)

- ledipasvir–sofosbuvir once daily for 24 weeks (n=217).

Randomisation was stratified by HCV genotype 1 subtype (1a or 1b) and the presence or absence of cirrhosis. The company stated that the baseline patient characteristics were generally balanced among the 4 treatment groups. People were assessed for up to 24 weeks after treatment stopped.

3.3 ION-3 was a multicentre (59 centres in the USA), open-label, non-randomised controlled trial in 647 adults with treatment-naive genotype 1 HCV without cirrhosis. The treatment groups that supported the dosage in the UK marketing authorisation were:

- ledipasvir–sofosbuvir for 8 weeks (n=215)
- ledipasvir–sofosbuvir for 12 weeks (n=216).

Randomisation was stratified by HCV genotype 1 subtype (1a or 1b). The company stated that the baseline patient characteristics were generally balanced across the treatment groups. People were assessed for up to 24 weeks after treatment stopped.

3.4 The primary outcome measure of both ION-1 and ION-3 was sustained virological response 12 weeks after stopping treatment (SVR12). A 'full analysis set' population was used to analyse the efficacy outcomes for both trials (that is, people who were randomised into the study and had at least 1 dose). The results were compared with an 'adjusted' historical control rate of 60% for SVR12 with peginterferon alfa-2a and ribavirin taken from phase III telaprevir (ADVANCE) and boceprevir (SPRINT-2) studies. In both studies, each treatment group had an SVR12 superior to the historical control rate of 60% ($p<0.001$ for all comparisons). The results for the populations of interest are given in table 2. All people who had an SVR12 also had an SVR24 in both trials (that is, all those whose HCV had a sustained virological response 12 weeks

after treatment maintained sustained virological response 24 weeks after treatment).

Table 2 Sustained virological response rates at 12 weeks for ledipasvir–sofosbuvir in people with HCV genotype 1

Patient population	Subgroup	Duration (weeks)	Study	SVR12 % (n/N)
Genotype 1 HCV without cirrhosis	Treatment-naive	8	ION-3	94.0 (202/215)
		12	ION-3	96.3 (208/216)
			ION-1	99.4 (179/180)
	Treatment-experienced	12	ION-2	95.4 (83/87)
		24	ION-2	98.9 (86/87)
Genotype 1 HCV with compensated cirrhosis	Treatment-naive	12	ION-1	94.1 (32/34)
		24	ION-1	97.0 (32/33)
	Treatment-experienced	12	ION-2	86.4 (19/22)
		24	ION-2	100 (22/22)
			SIRIUS	97.4 (75/77)

SVR, sustained virological response
Treatment-naive – the person has not had treatment for chronic hepatitis C
Treatment-experienced – the person's hepatitis C has not adequately responded to either peginterferon plus ribavirin or peginterferon plus ribavirin plus a protease inhibitor.

3.5 Pre-specified subgroup analyses of ION-1 were done based on patient characteristics and the randomisation strata. The company stated that high SVR12 rates were seen in people with characteristics historically associated with poor response including: cirrhosis, genotype 1a (which is considered harder to treat than 1b), a single nucleotide polymorphism without 2 copies of the C allele near their IL28B gene (that is, non-CC genotype IL28B polymorphism), and specific ethnic groups.

3.6 Pre-specified subgroup analyses of ION-3 were based on patient characteristics and the randomisation strata. The SVR12 rates in people who had ledipasvir–sofosbuvir for 8 weeks ranged from 89–100% in all subgroups. The company commented that the SVR12

rates in pre-specified subgroups, including those historically associated with poor response to interferon treatment, were similar to those seen in the overall population, across the treatment groups. The company also did a post-hoc analysis of relapse rates associated with baseline HCV ribonucleic acid (RNA). This analysis showed that:

- **For people with baseline HCV RNA of less than 6 million IU/ml** (viral load, or the number of virus particles in the blood; a viral load less than 6 million IU/ml has been linked to better response to treatment) relapse rates were similar between the 8-week (2 of 121 people; 2%) and 12-week (2 of 128 people; 2%) ledipasvir–sofosbuvir treatment groups.
- **For people with baseline HCV RNA of 6 million IU/ml or more**, the relapse rates were different between the 8-week (9 of 92 people; 10%) and 12-week (1 of 82 people; 1%) ledipasvir–sofosbuvir treatment groups.

The company concluded that these data supported the use of 8 weeks' ledipasvir–sofosbuvir in people with treatment-naive genotype 1 HCV without cirrhosis and a baseline viral load of less than 6 million IU/ml.

Genotype 1: Treatment-experienced HCV

3.7 ION-2 was a multicentre (64 centres in USA), open-label phase III non-randomised controlled trial in 440 adults with previously-treated genotype 1 HCV. The treatment arms that supported the dosage in the UK marketing authorisation were:

- ledipasvir–sofosbuvir for 12 weeks (n=109)
- ledipasvir–sofosbuvir for 24 weeks (n=109)

Randomisation was stratified by HCV genotype 1 subtype (1a or 1b), the presence or absence of cirrhosis, and response to previous

treatment (relapse or virologic breakthrough compared with no response). The company stated that the baseline patient characteristics were generally balanced across the treatment groups, but there were differences in age between treatment groups (p=0.02). People were assessed for up to 24 weeks after treatment stopped.

3.8 The primary outcome measure of ION-2 was SVR12. A 'full analysis set' population was used to analyse the efficacy outcomes. The results were compared with an 'adjusted' historical control rate of 25% for SVR12 in a population with previously-treated HCV, based on data from phase III telaprevir (REALIZE) and boceprevir (RESPOND-2) studies. Each treatment group had a higher SVR12 than the historical rate of 25% ($p<0.001$ for all comparisons). The results for the populations of interest are presented in table 2. All people who had an SVR12 also had an SVR24.

3.9 Pre-specified subgroup analyses were done based on patient characteristics and the randomisation strata. The company stated that high SVR12 rates were seen independent of HCV genotype 1 subtype, previous treatment option and response to previous treatment. The company highlighted that in people with cirrhosis there was a difference (p=0.007) in SVR12 between the 12-week (82–86%) and 24-week (100%) treatments (of note, both of these treatment durations are specified in the marketing authorisation). However, the company stated this observation should be considered preliminary because ION-2 was not powered for intergroup comparisons. For people previously treated with peginterferon plus ribavirin, SVR12 was between 93.0% and 100.0%. For people previously treated with a protease inhibitor plus peginterferon and ribavirin, the SVR12 was between 93.9% and 98%.

Genotype 3

3.10 ELECTRON-2 is an ongoing, multicentre (2 centres in New Zealand), open-label, non-randomised controlled trial in adults with genotypes 1, 3 or 6 HCV. It included the following treatment groups, relevant to this appraisal:

- People with treatment-naive genotype 3 HCV (with or without cirrhosis) who had ledipasvir–sofosbuvir plus ribavirin for 12 weeks (n=26).
- People with treatment-experienced genotype 3 HCV (with or without cirrhosis) who had ledipasvir–sofosbuvir plus ribavirin for 12 weeks (n=50).

The primary outcome was SVR12. However, at the time of evidence submission the company only had data from an interim analysis for the treatment-experienced genotype 3 HCV population that reported SVR4. A 'full analysis set' population was used to analyse the efficacy outcomes. No statistical hypothesis testing was done. The results for each population are presented in table 3.

Table 3 Sustained virological response rates for 12 weeks' ledipasvir–sofosbuvir plus ribavirin in people with genotype 3 HCV in ELECTRON-2

Patient population	Subgroup	SVR % (n/N)
Genotype 3 HCV without cirrhosis	Treatment-naive	SVR12: 100 (21/21)
	Treatment-experienced	SVR4: 89 (25/28)†
Genotype 3 HCV with compensated cirrhosis	Treatment-naive	SVR12: 100 (5/5)
	Treatment- experienced	SVR4: 77 (17/22)†

SVR: sustained virological response

Treatment-naive – the person has not had treatment for chronic hepatitis C
Treatment-experienced – the person's hepatitis C has not adequately responded to interferon-based treatment

† The company's response to clarification presented SVR12 data for people with treatment-experienced HCV genotype 3 (82%; 41/50), but did not present the SVR12 data by cirrhosis status

3.11 Ledipasvir–sofosbuvir with or without ribavirin for 24 weeks was not studied in ELECTRON-2. However, because of the limited clinical data available for the genotype 3 HCV population, ledipasvir–sofosbuvir's marketing authorisation recommends that 24 weeks of therapy (combined with ribavirin) is advised in 'all patients with treatment-experienced HCV genotype 3' and 'those patients with treatment-naive HCV genotype 3 with cirrhosis', to be conservative. No recommendations about treatment duration and the use of ribavirin are presented in the ledipasvir–sofosbuvir summary of product characteristics for treatment-naive genotype 3 HCV in people without cirrhosis, but the company has included this population in its economic model (assuming a 12-week treatment duration).

Genotype 4

3.12 The company stated that only limited data are currently available in people with genotype 4 HCV, from 2 studies:

- ION-1, 2 people with genotype 4 HCV were enrolled; 1 had ledipasvir–sofosbuvir for 12 weeks and 1 had ledipasvir–sofosbuvir plus ribavirin for 24 weeks. Both people had an SVR12.
- SYNERGY, a multicentre, open-label phase II non-randomised controlled trial evaluating ledipasvir–sofosbuvir for 12 weeks in adults with genotypes 1 or 4 HCV. The SVR data from SYNERGY cannot be presented here because the company labelled the data as commercial in confidence.

The company stated that genotype 1 and 4 HCV infections respond to HCV treatments similarly. Therefore, it was recommended in the ledipasvir–sofosbuvir summary of product characteristics that these genotypes are treated similarly.

People with advanced liver disease and after liver transplant

3.13 SOLAR-1 is an ongoing multicentre (30 centres in the USA), open-label, phase II, non-randomised controlled trial in adults with genotypes 1 or 4 HCV, and either advanced liver disease or who have had a liver transplant. People were randomised to have ledipasvir–sofosbuvir plus ribavirin for 12 weeks or ledipasvir–sofosbuvir plus ribavirin for 24 weeks. The SVR data from SOLAR-1 cannot be presented here because the company labelled the data as commercial in confidence.

People co-infected with HIV

3.14 ERADICATE is an ongoing US single-centre, open-label, phase II, study in adults with treatment-naive genotype 1 HCV co-infected with HIV and without cirrhosis. People were allocated to 2 treatment groups of ledipasvir–sofosbuvir for 12 weeks based on whether or not they had received antiretroviral therapy for their HIV. SVR12 was reported in 49 of 50 people (98%, 95% confidence interval [CI] not reported). For people who had not taken antiretroviral therapy before, SVR12 was reported in 13 out of 13 people (100%, 95% CI 75 to 100%). For people who had taken antiretroviral therapy before, SVR12 was reported in 36 out of 37 people (97%, 95% CI 89 to 100%).

Health-related quality of life

3.15 Four health-related quality-of-life questionnaires were used in ION-1, ION-2 and ION-3: Short Form 36 Health Survey (SF-36), Chronic Liver Disease Questionnaire (CLDQ-HCV), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Work Productivity and Activity Impairment Questionnaire (WPAI). The company considered that the responses to these 4 questionnaires suggested that ledipasvir–sofosbuvir alone does not generally worsen a person's health-related quality of life between baseline

and end of treatment, but a person's health-related quality of life reduces with addition of ribavirin. The company considered that the mean responses of these 4 questionnaires generally improved from the end of treatment to 12 weeks after treatment.

Adverse effects of treatment

3.16 The company presented data on adverse reactions from ION-1, ION-2 and ION-3. Across all the treatment groups in these studies, at least 67% of people had at least 1 adverse reaction. Higher rates were generally seen in treatment groups of longer duration and those including ribavirin. The most common adverse reactions in people having ledipasvir–sofosbuvir (with or without ribavirin) were fatigue, headache, insomnia and nausea. However, people taking ledipasvir–sofosbuvir with ribavirin had higher rates of adverse reactions known to be associated with ribavirin therapy, compared with people taking ledipasvir–sofosbuvir without ribavirin. These included anaemia, cough, fatigue, headache, insomnia, irritability, nausea, pruritus and rash. Most adverse reactions were mild to moderate in severity (grade 1 or 2, the range reported across all treatment groups was 90.2% to more than 99%). Ten of 865 people in ION-1 stopped treatment because of adverse reactions (all 10 people had an SVR12). No one in ION-2, and 3 of 647 people in ION-3 (the number of these who had an SVR12 was not reported by the company) stopped treatment because of adverse reactions. No deaths were reported in the studies.

Meta-analysis and mixed treatment comparison

3.17 The company did not do a meta-analysis of the available clinical studies.

3.18 The company did not do a mixed treatment comparison to compare the relative effectiveness of ledipasvir–sofosbuvir with the comparators listed in the scope of the appraisal. It stated that it was

not possible because the evidence for ledipasvir–sofosbuvir came from studies evaluating different treatment durations and without control groups. Therefore it could not identify a common comparator that would allow it to create a network. The company commented that whereas the lack of a mixed treatment comparison may be considered a limitation:

- SVR is a hard and objective end point consistently measured across all studies, and is not subject to bias from the patient or investigator.
- The baseline characteristics of the study populations were similar except for a higher proportion of people with cirrhosis and HCV genotype 1 subtype 1a in the ledipasvir–sofosbuvir studies, both of which the company considered to be historically associated with numerically lower SVR rates.

Cost effectiveness

3.19 The company submitted a Markov state-transition model that reflected the natural history of chronic hepatitis C. It compared ledipasvir–sofosbuvir (with or without ribavirin) with the comparators defined in the final scope of the appraisal. The company's economic model had 9 states, according to disease stage and treatment response. The same model structure was used for all people irrespective of HCV genotype or treatment experience. The company used a monthly cycle length for the first 18 cycles, then 3-monthly until year 2 and yearly thereafter. The company did the economic analysis from an NHS and personal social services perspective and chose a lifetime time horizon (from age 40 [for treatment-naive HCV] or 45 [for treatment-experienced HCV] until people reached 100 years). Costs and health effects were discounted at an annual rate of 3.5% and a half-cycle correction was applied from year 3.

3.20 The cost effectiveness of ledipasvir–sofosbuvir was assessed in populations defined by HCV genotype, which included those with cirrhosis (but excluded HIV co-infection):

- treatment-naive genotype 1 HCV
- treatment-naive genotype 4 HCV
- treatment-experienced genotypes 1 and 4 HCV
- treatment-naive genotype 3 HCV
- treatment-experienced genotype 3 HCV, unsuitable for interferon therapy.

The company did not include people with treatment-experienced genotype 3 HCV that was suitable for interferon therapy because it considered that it was unlikely that 24-week ledipasvir–sofosbuvir would be cost effective compared with 12-week sofosbuvir plus peginterferon alfa and ribavirin (given the higher treatment costs with ledipasvir–sofosbuvir and no evidence of additional efficacy).

3.21 The company used patient characteristics from the HCV Research UK database to inform the mean age, the proportion with cirrhosis, and weight of the population entering the model. People entered the model in either the non-cirrhotic or compensated cirrhosis stages of disease. People who started treatment in the non-cirrhotic state and were cured would not become symptomatic again. However, people with cirrhosis whose HCV was cured were still at risk of progression to the decompensated cirrhosis and hepatocellular carcinoma state. Those who did not clear the virus after treatment remained in their respective health states, or progressed to more severe stages of chronic HCV. All people in the decompensated cirrhosis health state were assumed to be candidates for liver transplant. The company chose transition probabilities for disease progression from several publications used in recent NICE technology appraisals of treatments for HCV

(Cardoso et al. 2010; Fattovich et al. 1997; Grishchenko et al. 2009; Hartwell et al. 2011; Shepherd et al. 2007; Siebert et al. 2005; Thompson et al. 2008). Transition probabilities from the non-cirrhotic to cirrhotic health state varied according to age and genotype according to published literature. Age- and sex-specific general population mortality was also applied to each health state in the company's model.

3.22 Treatment-effect data for ledipasvir–sofosbuvir were based on SVR12 from the relevant ION studies and ELECTRON-2 (except for the genotype 3 treatment-experienced HCV population for whom only SVR4 data were available). Treatment-effect data for the comparators were taken from publications or the summary of product characteristics. Because there was no mixed treatment comparison (see section 3.19), the estimates of the relative effectiveness of ledipasvir–sofosbuvir with the comparators were based on naive indirect comparisons. In its base-case analysis the company used the ledipasvir–sofosbuvir data from the genotype 1 HCV population for the analysis of the genotype 4 HCV population because:

- the data available for ledipasvir–sofosbuvir in genotype 4 HCV were limited
- the ledipasvir–sofosbuvir summary product of characteristics states that genotype 1 and 4 HCV infections are generally treated in the same way.

The company commented that the cost-effectiveness analysis for the treatment-experienced population considered genotypes 1 and 4 HCV together. However, for the treatment-naive HCV population, 8 weeks of ledipasvir–sofosbuvir is only recommended for treatment-naive genotype 1 HCV without cirrhosis (people with genotype 4 HCV are treated with 12 weeks of ledipasvir–sofosbuvir

only). Therefore, separate analyses were done for treatment-naive genotypes 1 and 4 HCV in this population. The company explored genotype 4 data in a scenario analysis. If more than 1 treatment duration was recommended for a given genotype in the ledipasvir-sofosbuvir summary of product characteristics (based on certain patient or clinical characteristics), the company used a weighted-average of the efficacy and treatment duration data in the cost-effectiveness analysis (rather than presenting the results for each regimen of ledipasvir–sofosbuvir separately; also referred to as a 'blended comparison').

3.23 Resource use and costs in the company's economic model included those for treatment (drug and administration), monitoring during treatment, adverse reactions and for each health state (that is, monitoring of people after treatment has stopped). Drug costs were based on the list prices in the 'British national formulary' (BNF; August 2014). Monitoring costs were based on NHS reference costs, published literature or the company's clinical expert opinion (if a published source was unavailable). An additional cost for an 'initial patient evaluation' was included for people with treatment-naive HCV, but the monitoring requirements for people having interferon-containing treatments or interferon-free treatments did not differ. Treatment durations were also used to estimate drug and monitoring costs, and the proportion of people on a given treatment duration were generally based on the company's clinical expert opinion. Costs for each of the health states in the company's economic model were taken from the published literature (Grishchenko et al. 2009; Longworth et al. 2014; Wright et al. 2006) and inflated to 2012–13 prices. Adverse reaction costs were taken from the BNF and NHS reference costs. The company assumed that the cost of each adverse reaction also

depended on whether the reaction is actively treated in an outpatient setting, by a hospital registrar or specialist.

3.24 To estimate the health-related quality of life, the company used EQ-5D utility values from Wright et al. (2006) that were based on a UK trial of mild chronic hepatitis C. For people who had an SVR, the company's economic model included a utility benefit of 0.04 taken from Vera-Llonch et al. (2013). The company's economic model also captured the health-related quality of life of people while 'on-treatment' (independent of whether they had cirrhosis or not). The company assumed that the health-related quality of life of people treated with ledipasvir–sofosbuvir without ribavirin did not change while 'on-treatment', but reduced in people having treatments that included ribavirin or interferon. The company stated that these 'on-treatment' decrements were assumed to include any effect on health-related quality of life from treatment-related adverse reactions.

3.25 The company's deterministic cost-effectiveness results for ledipasvir–sofosbuvir compared with the comparators for each population and ordered by cost are given in tables 4–8.

Table 4 Incremental cost-effectiveness results for treatment-naive genotype 1 HCV

Treatment option	Total			ICER (£/QALY gained)
	Cost	LY	QALY	
No treatment	£18,956	18.30	13.01	–
PR	£25,308	19.23	13.98	£6548
LDV-SOF	£38,713	20.81	15.66	£7985
SMV+PR	£38,731	20.14	15.02	Dominated
TVR+PR	£40,237	19.99	14.85	Dominated
BOC+PR	£41,299	19.93	14.66	Dominated
SOF+PR	£45,776	20.54	15.40	Dominated
SOF+SMV	£65,630	20.74	15.57	Dominated

BOC, boceprevir; LDV, ledipasvir; LY, life years; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year, ICER, incremental cost-effectiveness ratio; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir

Dominated, fewer QALYs at greater cost than comparator

Table 5 Incremental cost-effectiveness results for treatment-naive genotype 4 HCV

Treatment option	Total			ICER (£/QALY gained)
	Cost	LY	QALY	
No treatment	£18,956	18.30	13.01	–
PR	£25,308	19.23	13.98	£6548
SMV+PR	£38,731	20.14	15.02	Extended dominance
SOF+PR	£45,776	20.54	15.40	Extended dominance
LDV-SOF	£46,823	20.81	15.67	£12,715
SOF+SMV	£65,630	20.74	15.57	Dominated

LDV, ledipasvir; LY, life years; PR, pegylated interferon+ribavirin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SMV, simeprevir; SOF, sofosbuvir
Dominated, fewer QALYs at greater cost than comparator.
Extended dominance, a combination of 2 of its comparators provides equal health at a reduced cost.

Table 6 Incremental cost-effectiveness results for treatment-experienced genotype 1 and 4 HCV

Treatment option	Total			ICER (£/QALY gained)
	Cost	LY	QALY	
No treatment	£18,143	17.44	12.40	–
PR	£24,960	17.83	12.75	Extended dominance
TVR+PR*	£42,101	18.84	13.90	Extended dominance
SMV+PR*	£43,626	19.17	14.13	Extended dominance
BOC+PR	£45,897	18.62	13.69	Dominated
SOF+PR	£46,756	19.16	14.21	Extended dominance
LDV-SOF	£49,537	19.58	14.72	£13,527
SOF+SMV	£64,720	19.60	14.71	Dominated

BOC, boceprevir; LDV, ledipasvir; LY, life years; PR, pegylated interferon+ribavirin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
Dominated, fewer QALYs at greater cost than comparator.
Extended dominance, a combination of 2 of its comparators provides equal health at a reduced cost.
* TVR and BOC have a UK marketing authorisation for people with HCV genotype 1 only.

Table 7 Incremental cost-effectiveness results for treatment-naive genotype 3 HCV

Treatment option	Total			ICER (£/QALY gained)
	Cost	LY	QALY	
With and without cirrhosis				
PR	£18,937	19.07	14.01	–
No treatment	£21,509	17.49	12.24	Dominated
LDV-SOF+R	£57,909	20.76	15.48	£26,491
With cirrhosis				
SOF+PR	£63,419	16.28	9.38	–
SOF+R	£95,947	17.04	9.87	Extended dominance
LDV-SOF+R	£102,645	17.55	10.23	£46,491

LDV, ledipasvir; LY, life years; PR, pegylated interferon+ribavirin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; R, ribavirin; SOF, sofosbuvir.
Dominated, fewer QALYs at greater cost than comparator.
Extended dominance, a combination of 2 of its comparators provides equal health at a reduced cost.

Table 8 Incremental cost-effectiveness results for treatment-experienced genotype 3 HCV unsuitable for interferon therapy

Treatment option	Total			ICER (£/QALY gained)
	Cost	LY	QALY	
With and without cirrhosis				
No treatment	£20,614	16.74	11.71	–
LDV-SOF+R	£89,522	19.10	14.17	£28,048
With cirrhosis				
SOF+R	£101,109	14.13	8.01	
LDV-SOF+R	£105,761	15.24	8.76	£6210

LDV, ledipasvir; LY, life years; PR, pegylated interferon+ribavirin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; R, ribavirin; SOF, sofosbuvir.

3.26 For most comparisons, ledipasvir–sofosbuvir resulted in lower costs 'off-treatment' because it was associated with better efficacy (because there was a higher probability of cure, fewer people move to more expensive severe health states). For some comparisons (particularly in treatment-naive genotype 1 HCV), ledipasvir–sofosbuvir was also associated with lower 'on-treatment' costs because of shorter treatment duration and less intensive monitoring. Across all populations, a higher number of quality-adjusted life years (QALYs) were gained with ledipasvir–sofosbuvir

treatment than with the comparators. The company stated that this is because ledipasvir–sofosbuvir is associated with a higher probability of cure and therefore more people enter the SVR health state (associated with improved health-related quality of life) and fewer people progress to the more severe health states (associated with poorer health-related quality of life).

3.27 The company presented results of a one-way sensitivity analysis for ledipasvir–sofosbuvir compared with each of the comparators for each population (see section 3.20). The one-way sensitivity analyses showed that the company's incremental cost-effectiveness ratios (ICERs) for ledipasvir–sofosbuvir were most sensitive to changes to the 'on-treatment' costs for people without cirrhosis, the discount rates used for costs and outcomes, the SVR rates of ledipasvir–sofosbuvir and the comparators, and the transition probability from the non-cirrhotic to the compensated cirrhosis health state.

3.28 The company did a scenario analysis using genotype 4 clinical data. For people with treatment-naive genotype 4 HCV, the company's ICER comparing ledipasvir–sofosbuvir with no treatment decreased from £10,468 to £9925 per QALY gained, but when using a fully incremental analysis the company's ICER for ledipasvir–sofosbuvir increased from £12,715 (compared with pegylated interferon plus ribavirin) to £17,390 per QALY gained (compared with simeprevir plus pegylated interferon and ribavirin). For people with treatment-experienced genotype 4 HCV, the company's ICER comparing ledipasvir–sofosbuvir with no treatment decreased from £13,527 to £12,313 per QALY gained, and when using a fully incremental analysis the company's ICER for ledipasvir–sofosbuvir decreased from £13,527 (compared with no treatment) to £12,313 per QALY gained (compared with no treatment).

3.29 The company also presented results from probabilistic analyses for each population. The probability of ledipasvir–sofosbuvir being cost effective compared with all comparator technologies at £20,000 and £30,000 per QALY gained is given in table 9.

Table 9 Company's probabilistic sensitivity analyses results

Population	Probability of being less than £20,000 per QALY gained	Probability of being less than £30,000 per QALY gained
Treatment-naive genotype 1 HCV	100%	100%
Treatment-naive genotype 4 HCV	88%	100%
Treatment-experienced genotypes 1 and 4 HCV	88%	100%
Treatment-naive genotype 3 HCV	2.5%	68%
Treatment-naive genotype 3 HCV with compensated cirrhosis	2.1%	8%
Treatment-experienced genotype 3 HCV, unsuitable for interferon therapy	1.4%	59.8%
Treatment-experienced genotype 3 HCV, unsuitable for interferon therapy, with compensated cirrhosis	78%	83%
HCV, hepatitis C virus		

3.30 The company presented ICERs for the subgroups of people without cirrhosis and with compensated cirrhosis (see table 10). The company commented that the cost effectiveness may vary in people with cirrhosis because of differences in efficacy and treatment duration of ledipasvir–sofosbuvir or comparator treatments.

Table 10 Summary of the company's base-case cost-effectiveness results and cost-effectiveness results by cirrhosis status (£/QALY gained)

Indication	Base case	Non-cirrhotic	Cirrhotic
Genotype 1 treatment naive HCV			
SOF+PR	LDV/SOF dominates	LDV/SOF dominates	£149
SMV+PR	LDV/SOF dominates	LDV/SOF dominates	£3156
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
BOC+PEG-IFN2b+RBV	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
TVR+PEG-IFN2a+RBV	LDV/SOF dominates	LDV/SOF dominates	£1522
PEG-IFN2a+RBV	£7985	£10,397	£4731
No treatment	£7458	£8965	£4920
Genotype 4 treatment naive HCV			
SOF+PR	£3869	£6790	£1349
SMV+PR	£12,399	£23,136	£3156
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
PEG-IFN2a+RBV	£12,715	£18,555	£4731
No treatment	£10,468	£13,734	£4920
Genotype 1 and 4 treatment experienced HCV			
SOF+PR	£5497	£3011	£11,001
SMV+PR	£9984	£10494	£9102
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	SW quadrant*
BOC+PEG-IFN2b+RBV†	£3551	£5748	£1265
TVR+PEG-IFN2a+RBV†	£9144	£13,741	£4303
PEG-IFN2a+RBV	£12,491	£16,125	£6666
No treatment	£13,527	£17,205	£7415
Genotype 3 treatment naive HCV (LDV/SOF+RBV)			
SOF+PR	£46,491	NA	£46,491
SOF+RBV	£19,013	NA	£19,013
PR	£26,491	£39,149	£17,622
No treatment	£11,235	£10,549	£12,335

Indication	Base case	Non-cirrhotic	Cirrhotic
Genotype 3 treatment experienced HCV (LDV/SOF+RBV)			
SOF+RBV	£6210	NA	£6210
No treatment	£28,048	£33,631	£18,252

BOC, boceprevir; GT, genotype; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; PEG-IFN, pegylated interferon; QALY; quality adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
* South West quadrant: ledipasvir–sofosbuvir results in cost savings but fewer QALYs.
† TVR and BOC have a UK marketing authorisation for people with genotype 1 HCV only.
Note: The company's ICERs for the subgroup analysis presented in table 11 are for ledipasvir–sofosbuvir compared with the reference comparator from the company's base-case incremental analysis. If the company did an incremental analysis for its subgroup analysis, it may indicate alternative comparators.

3.31 The company did not present ICERs for the following subgroups included in the final scope of the appraisal.

- **People co-infected with HIV:** The company did not model the co-infected HIV population separately because it considered that the efficacy and safety of ledipasvir–sofosbuvir treatments for people co-infected with HIV and HCV is similar to that seen in people with HCV mono-infection, and as such is treated in the same way. The company stated this approach was validated by its clinical experts and was conservative because HCV–HIV co-infection is likely to progress to severe health states more quickly if left untreated than HCV mono-infection.
- **People who had treatment before and after liver transplant:** The company did not model this subgroup because of a lack of clinical data.
- **People whose HCV had responded to previous treatment:** The company did not consider this subgroup to be relevant because response to interferon-free treatments (such as ledipasvir-sofosbuvir) is not affected by previous response to interferon-containing treatments.

ERG comments on the clinical effectiveness

3.32 The ERG considered that it was unlikely that any studies of ledipasvir–sofosbuvir relevant to this appraisal were missed. However, the ERG noted that there were some major gaps in the reporting of the searches done by the company, and the company's searches for comparator and adverse events were not systematic.

3.33 The ERG stated that although the 3 phase III studies were open-label, they were generally at low risk of bias. It commented that the phase II studies had small sample sizes but provided data consistent with the phase III trials. The ERG stated, however, that subjective health-related quality-of-life outcomes were subject to bias.

3.34 The ERG noted that historical controls were used because there was no control arm. It commented that there are limitations with using historical controls, particularly when there are changes in the definition of, or diagnostic methods used to detect, the condition under consideration. However, the ERG stated this was unlikely to be an issue for hepatitis C, and that their clinical expert advised that the use of historical controls in this context was considered to be reasonable.

3.35 The ERG's clinical experts suggested that the diagnostic criteria used for the disease and the SVR outcomes used in the studies were representative of clinical practice in England. The ERG commented that the use of SVR12 was appropriate because there is a high correlation between SVR12 and SVR24. However, it noted that SVR4 is not a suitable surrogate end point for cure because there is a chance of relapse between 4 and 12 weeks.

3.36 The ERG highlighted that the results of the company's subgroup analyses for factors not stratified at randomisation were potentially

biased because the respective subgroups may not be well-balanced across treatment arms.

3.37 The ERG commented that ION-1 (people with cirrhosis) and ION-3 could create a network of evidence, although without any links to the comparator treatments. The ERG considered it would have been useful for the company to:

- analyse the 6 treatment arms from these studies and estimate the joint posterior distribution of treatment effect (for example, odds ratios), because it is reasonable to assume that the effectiveness of ledipasvir–sofosbuvir depends on treatment duration
- synthesise the evidence for each comparator (for example, the company acknowledged that a meta-analysis was possible for estimating the SVR rates for boceprevir, pegylated interferon plus ribavirin, simeprevir and telaprevir in people with genotype 1 HCV).

3.38 The ERG commented that the efficacy of ledipasvir–sofosbuvir does not appear to depend on the patient characteristics prespecified in the company's subgroup analyses. However, given that several patient characteristics were prespecified, it seems reasonable to assume that these characteristics may affect the efficacy of some comparators. The ERG concluded that in a given study, SVR rates for comparator treatments are much more likely to vary compared with SVR rates for ledipasvir–sofosbuvir (that is, using SVR rates from a single comparator study introduces more uncertainty than using SVR rates for ledipasvir–sofosbuvir from a single study).

3.39 The ERG's clinical experts stated that HCV genotype 1 subtype 1a, baseline viral load and IL28B CC genotype had less effect on

response to treatment with ledipasvir–sofosbuvir compared with current treatment options. The ERG's clinical experts advised that there was unlikely to be any meaningful differences in baseline characteristics between the populations of the ledipasvir–sofosbuvir and comparator studies that would significantly affect outcomes. The ERG concluded that although baseline characteristics appear similar between intervention and comparator trials, the possibility that other factors differed across trials cannot be ruled out (see section 3.49).

ERG comments on the cost effectiveness

3.40 The ERG considered that the company's model structure was broadly appropriate and in line with previous economic analyses of treatments for hepatitis C.

3.41 The ERG's clinical experts noted that people with genotype 3 HCV and cirrhosis have active treatment because of disease severity. Therefore, it considered that the company's exclusion of 'no treatment' as a comparator for these populations was appropriate.

3.42 The ERG stated that boceprevir and telaprevir do not have a UK marketing authorisation for treating genotype 4 HCV and should not be considered as comparators for this population.

3.43 The ERG commented that it was unclear whether the baseline proportion of people with cirrhosis used in the company's model reflects the HCV population in England.

3.44 The ERG commented that the details about how transition probabilities from the non-cirrhotic to the compensated cirrhosis health states had been estimated were insufficient for the ERG to critique the robustness of the approach. The ERG highlighted that the transition probabilities from compensated or decompensated cirrhosis to hepatocellular carcinoma were considerably higher for

this appraisal (0.0631; Cardoso et al. 2010) than those used by the same company in its economic model for sofosbuvir for treating chronic hepatitis C (0.014; Fattovich et al. 1997).

3.45 The ERG commented that the company's assumption that people cannot die or have disease progression until 12–24 weeks after completing treatment lacks credibility. However, the ERG acknowledged that the size of bias was likely to be small and would favour treatment options given over longer treatment durations.

3.46 The ERG highlighted that using SVR4 data for the genotype 3 HCV population is likely to overestimate the effectiveness of ledipasvir–sofosbuvir (see sections 3.23 and 3.35).

3.47 The ERG noted that the selection criteria for comparator SVR rates in the company's economic model were not clear, and that the company's submission did not indicate the range of SVR estimates possible for the comparators. The ERG stated that because the SVR rates for comparators were estimated from single studies, rather than a meta-analysis of all relevant studies, it was not clear whether they were conservative or optimistic rates. The ERG commented that using naive indirect comparisons breaks randomisation and fails to fully reflect uncertainty around the SVR rates. The ERG concluded that the cost-effectiveness results may be biased by the selection of individual studies and confounded by the effect of other factors such as differences in study design, patient characteristics and trial protocols.

3.48 The ERG stated that the results should be interpreted with caution when using the company's weighted-average approach (that is, the company included more than 1 treatment duration of ledipasvir–sofosbuvir within its base-case analysis for some populations listed in section 3.20 [for example, treatment-naive genotype 1 HCV] and therefore the efficacy and cost inputs used in the model depended

on the assumed proportion of people receiving each treatment duration). The ERG also noted that the company's submission did not explicitly state the treatment durations estimated from the company's weighted-average approach. The ERG concluded that using cost-effectiveness results dependent on the company's weighted-average approach may result in the recommendation of some options that represent an inefficient use of NHS resources, particularly when taking into account that there may be clear clinical reasons why specified treatment durations of ledipasvir–sofosbuvir should be considered for specific subgroups of people.

3.49 The ERG highlighted that for people with treatment-naive genotype 1 HCV, the company used a 79% to 21% split between the 8-week and 12-week ledipasvir–sofosbuvir treatments. This was because data from the HCV Research UK database showed that 79% of this population had a pre-treatment viral load less than 6 million IU/ml (based on the company's post-hoc subgroup analysis, the company stated this group is likely to have 8-week treatment; see section 3.7). However, the ERG considered that this criterion is not consistent with the recommendations for this treatment indication in the ledipasvir–sofosbuvir marketing authorisation and is based on a post-hoc analysis of the ION-3 study.

3.50 The ERG considered that the company did not sufficiently explain how choices were made in the selection of costs and utility values used in its economic model, nor did the company specify the source used for resource use estimates.

3.51 The ERG commented that the publication (Vera-Llonch et al. 2013) used by the company to reflect the utility gain associated with achieving SVR was derived using a US EQ-5D tariff of 0.04. It suggested that the utility gain associated with an SVR taken from

Wright et al. (2006), which reflects the preferences of the general public in England (that is, using a UK EQ-5D tariff of 0.05) would be more appropriate. The ERG stated that the 'on-treatment' decrements used by the company were applied to the entire cycle in the 'on-treatment' health state rather than for the duration of treatment, but the ERG noted that the effect of this bias was likely to be small.

3.52 The ERG highlighted that health effects on people with HCV (that is, potential for reinfection) and health effects between people (that is, onward transmission) were excluded from the company's model. The ERG explained that:

- Excluding reinfection is likely to overestimate the health benefits of more effective treatments while underestimating their costs (because people may subsequently need retreatment).
- Excluding onward transmission may underestimate the health benefits of more effective treatments.

The ERG acknowledged that models used to inform previous NICE technology appraisals for treatments of chronic hepatitis C did not include such health effects and exploring this issue would need a different model structure. However, it concluded that it was concerned that the company's results were potentially unreliable because the effect on the cost-effectiveness results from these exclusions was unclear.

3.53 The ERG highlighted that the company's base-case analysis uses point estimates of parameters (that is, a deterministic approach) rather than the expectation of the mean (that is, a probabilistic approach). However, the ERG considered that the results from the deterministic analyses and probabilistic analyses were similar from the company's economic model.

3.54 The ERG considered that the results of the company's probabilistic analyses were limited because of:

- key uncertain parameters (for example, SVR rates) being pre-sampled outside of the model rather than sampling from a distribution
- the use of inappropriate distributions for some parameters.

3.55 The ERG presented ICERs for several exploratory analyses, using deterministic analyses because of the computation time and complexity associated with running probabilistic analyses. The ERG did the following additional analyses:

- Scenario 1: Developed an ERG-preferred base case exploring each recommended treatment duration for ledipasvir–sofosbuvir separately (that is, removing the company's weighted-average approach; see sections 3.23 and 3.48)
- Scenario 2: Explored the alternative recommended treatment durations for ledipasvir–sofosbuvir for specific subgroups of people (as stipulated in the marketing authorisation for ledipasvir-sofosbuvir)
- Scenario 3: Used alternative transition probabilities based on the sofosbuvir model (see section 3.44)
- Scenario 4: Used a UK-valued utility increment derived by Wright et al. (2006; see section 3.51)
- Scenario 5: Used shorter time horizons (5 years and 10 years) to test the assumptions around exclusion of health effects from reinfection (see section 3.52)
- Scenario 6: An analysis exploring the sensitivity of the ERG's ICERs to changing the SVR rates of the comparators used by the company.

Exploratory scenario analyses 3–6 used the ERG-preferred base-case analysis as a starting point, that is, they all also included scenario 1. The ERG also presented the results of the ERG's exploratory analyses separately for people with and without cirrhosis because the ledipasvir–sofosbuvir marketing authorisation makes recommendations specific to cirrhosis status.

Table 11 Summary of the ERG's incremental cost-effectiveness results for its exploratory scenario analysis 1 (and incremental ICERs for scenario 3 presented in column 5)

Treatment-naive genotype 1 HCV without cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF 12 weeks	17.20	£42,160	£22,676	£25,526
SOF+PEG-IFN2a+RBV	17.04	£41,082	Extended dominance	Extended dominance
SMV+PEG-IFN2a+RBV	16.81	£33,317	£16,601	£18,300
TVR+PEG-IFN2a+RBV	16.69	£34,631	Dominated	Dominated
BOC+PEG-IFN2b+RBV	16.41	£35,002	Dominated	Dominated
PEG-IFN2a+RBV	15.96	£19,205	£6939	£7572
No treatment	15.07	£13,029	-	-
Treatment-naive genotype 1 HCV with cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF 24 weeks	10.08	£101,052	£45,323	£79,899
SOF+PEG-IFN2a+RBV	9.25	£63,434	£5597	£6597
SMV+PEG-IFN2a+RBV	8.28	£59,098	Extended dominance	Extended dominance
BOC+PEG-IFN2b+RBV	8.09	£64,985	Dominated	Dominated
TVR+PEG-IFN2a+RBV	7.95	£61,326	Extended dominance	Dominated
PEG-IFN2a+RBV	6.54	£48,266	£5436	£6012
No treatment	5.25	£41,253	-	-
Treatment-naive genotype 4 HCV without cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF 12 weeks	17.20	£42,160	£22,676	£25,526
SMV+PEG-IFN2a+RBV	16.81	£33,317	£16,601	£18,300
PEG-IFN2a+RBV	15.96	£19,205	£6939	£7572
No treatment	15.07	£13,029	-	-
Treatment-naive genotype 4 HCV with cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF 24 weeks	10.08	£101,052	£45,323	£79,899
SOF+PEG-IFN2a+RBV	9.25	£63,434	£5597	£6597

SMV+PEG-IFN2a+RBV	8.28	£59,098	Extended dominance	Extended dominance
PEG-IFN2a+RBV	6.54	£48,266	£5436	£6012
No treatment	5.25	£41,253	-	-
Treatment-experienced genotype 1 or 4 HCV without cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF 12 weeks	16.11	£41,979	£16,566	£18,614
SOF+PEG-IFN2a+RBV*	15.71	£42,387	Dominated	Dominated
SMV+PEG-IFN2a+RBV	15.67	£38,730	Extended dominance	Extended dominance
TVR+PEG-IFN2a+RBV*	15.62	£36,460	Extended dominance	Extended dominance
BOC+PEG-IFN2b+RBV*	15.48	£39,911	Dominated	Dominated
PEG-IFN2a+RBV	14.61	£18,984	Extended dominance	Extended dominance
No treatment	14.31	£12,160	-	-
Treatment-experienced genotype 1 or 4 HCV with cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF 24 weeks	9.70	£99,222	£32,458	£57,385
SOF+PEG-IFN2a+RBV	8.59	£63,193	£6630	£8660
SMV+PEG-IFN2a+RBV	8.31	£62,046	Extended dominance	Extended dominance
TVR+PEG-IFN2a+RBV*	7.46	£63,325	Dominated	Dominated
BOC+PEG-IFN2b+RBV*	6.95	£68,413	Dominated	Dominated
PEG-IFN2a+RBV	5.74	£47,441	Extended dominance	Extended dominance
No treatment	5.19	£40,651	-	-
Treatment-naive genotype 3 HCV without cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF+RBV 24 weeks	17.24	£83,331	£88,853	£102,210
PEG-IFN2a+RBV	16.43	£11,360	-	-
No treatment	14.57	£14,928	Dominated	Dominated
Treatment-naive genotype 3 HCV with cirrhosis				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF+RBV 24 weeks	10.23	£102,645	£46,149	£79,825
SOF+RBV	9.87	£95,947	Extended dominance	Extended dominance
SOF+PEG-IFN2a+RBV	9.38	£63,419	£2363	£1392
No treatment	5.25	£41,253	-	-
Treatment-experienced genotype 3 HCV without cirrhosis, not suitable for interferon therapy				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF+RBV 24 weeks	15.97	£84,109	£33,576	£38,834
No treatment	13.88	£13,936	-	-
Treatment-experienced genotype 3 HCV with cirrhosis, not suitable for				

interferon therapy				
Option	QALYs	Costs	ICER	ICER (Scenario 3)
LDV/SOF+RBV 24 weeks	8.76	£105,761	£18,238	£30,495
SOF+RBV	8.01	£101,109	Extended dominance	Extended dominance
No treatment	5.19	£40,651	-	-

BOC, boceprevir; HCV, hepatitis C virus; LDV, ledipasvir; LY, life years; PEG-IFN+RBV, pegylated interferon+ribavirin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Dominated, fewer QALYs at greater cost than comparator.

Extended dominance, a combination of 2 of its comparators provides equal health at a reduced cost.

*not applicable for people with genotype 4 HCV

Table 12 Summary of the ERG's incremental cost-effectiveness results for its exploratory scenario analysis 2

Treatment-naive genotype 1 HCV without cirrhosis			
Option	QALYs	Costs	ICER
LDV/SOF 8 weeks	17.12	£29,523	£8894
SOF+PEG-IFN2a+RBV	17.04	£41,082	Dominated
SMV+PEG-IFN2a+RBV	16.81	£33,317	Dominated
TVR+PEG-IFN2a+RBV	16.69	£34,631	Dominated
BOC+PEG-IFN2b+RBV	16.41	£35,002	Dominated
PEG-IFN2a+RBV	15.96	£19,205	£6939
No treatment	15.07	£13,029	–
Treatment-naive genotype 1 HCV with cirrhosis			
Option	QALYs	Costs	ICER
LDV/SOF 12 weeks	9.94	£62,440	£4518
SOF+PEG-IFN2a+RBV	9.25	£63,434	Dominated
SMV+PEG-IFN2a+RBV	8.28	£59,098	Extended dominance
BOC+PEG-IFN2b+RBV	8.09	£64,985	Dominated
TVR+PEG-IFN2a+RBV	7.95	£61,326	Extended dominance
PEG-IFN2a+RBV	6.54	£48,266	Extended dominance
No treatment	5.25	£41,253	–
Treatment-experienced genotype 1/4 HCV without cirrhosis			
Option	QALYs	Costs	ICER
LDV/SOF 24 weeks	16.21	£80,577	£77,495
SOF+PEG-IFN2a+RBV*	15.71	£42,387	Extended dominance
SMV+PEG-IFN2a+RBV	15.67	£38,730	£45,396
TVR+PEG-IFN2a+RBV*	15.62	£36,460	£18,550
BOC+PEG-IFN2b+RBV*	15.48	£39,911	Dominated
PEG-IFN2a+RBV	14.61	£18,984	Extended dominance
No treatment	14.31	£12,160	–

Treatment-naive genotype 3 HCV without cirrhosis			
Option	QALYs	Costs	ICER
LDV/SOF 12 weeks	17.24	£42,997	£39,277
PEG-IFN2a+RBV	16.43	£11,360	–
No treatment	14.57	£14,928	Dominated

BOC, boceprevir; HCV, hepatitis C virus; LDV, ledipasvir; LY, life years; PEG-IFN+RBV, pegylated interferon+ribavirin; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
Dominated, fewer QALYs at greater cost than comparator.
Extended dominance, a combination of 2 of its comparators provides equal health at a reduced cost.
*not applicable for people with genotype 4 HCV

Equality

3.56 The company indicated that people with genotype 4 HCV represent a group with a particularly high unmet need, and that minority ethnic groups represent a higher proportion of people who have genotype 4 HCV than people who have genotypes 1 or 3 HCV in the UK. The company provided NICE with evidence from a HCV genotype surveillance report commissioned by the company to be produced by Public Health England. This showed that the proportion of people who were of white or white British family origin with genotype 1 or 3 HCV was 81% and 72% respectively, whereas minority ethnic groups represented 8% and 18% respectively. The proportion of people with genotype 4 HCV who were of white or white British family origin was 44%, whereas minority ethnic groups represented 39% (see table 13). Additionally, the company presented commercial-in-confidence evidence that a disproportionate number of people with HIV co-infection have genotype 4 HCV compared with people without HIV co-infection.

Table 13 Genotype by family origin

HCV genotype	White or white British (%)	Asian or Asian British (%)	Black or black British (%)	Other or mixed origin (%)	Unknown (%)
1	13675 (81)	875 (5)	116 (1)	265(2)	2023 (12)
2	1883 (84)	75 (3)	12 (1)	35 (2)	239 (11)
3	12001 (72)	2894 (17)	37 (0.22)	146 (0.88)	1532 (9)
4	593 (44)	378 (28)	48 (4)	90 (7)	239 (18)
5	25 (53)	7 (15)	6 (13)	0 (0)	9 (19)
6	12 (19)	4 (6)	1 (2)	42 (66)	5 (8)
Non-1	46 (70)	3 (5)	0 (0)	1 (2)	16 (24)
Dual	13 (59)	6 (27)	0 (0)	0 (0)	3 (14)
HCV; hepatitis C virus					

3.57 Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ledipasvir–sofosbuvir, having considered evidence on the nature of chronic hepatitis C and the value placed on the benefits of ledipasvir–sofosbuvir by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee heard from the clinical and patient experts about the nature of chronic hepatitis C. The patient expert stated that some people with chronic hepatitis C do not have any symptoms, but others may have chronic fatigue, mood swings and sexual dysfunction. The clinical and patient experts also commented that the psychological effect of having chronic hepatitis C can impair people's social life and ability to work, and that people can have anxiety about transmitting the virus. There is also stigma because of the association of chronic hepatitis C with drug use. The patient expert estimated that around 3% of the people infected with chronic hepatitis C take active treatment for their condition, but anticipated

that the availability of clinically-effective treatment options of short duration, such as ledipasvir–sofosbuvir, will encourage more people to seek diagnosis and treatment. In addition, the patient expert stated that people who use injectable drugs and whose hepatitis C is successfully treated were more likely than those whose hepatitis C was not treated to go on to address their drug use, leading to wider benefits to society. The Committee recognised the effect of chronic hepatitis C on the lives of people with the virus. It concluded that treatments that give very high levels of sustained virological response (which is considered equivalent to a cure), and that consequently help reduce the rate of hepatitis C virus (HCV) transmission and the stigma associated with having chronic hepatitis C, are of significant importance.

4.2 The Committee discussed the clinical management of chronic hepatitis C in adults. It heard from the clinical experts that treatment decisions and response to treatment are influenced by HCV genotype, level of liver damage, comorbidities and treatment history. The Committee was aware that ledipasvir–sofosbuvir has a marketing authorisation in the UK for adults with genotypes 1, 3 and 4 HCV. For people with genotype 1 HCV, the Committee heard that boceprevir plus peginterferon alfa and ribavirin or telaprevir plus peginterferon alfa and ribavirin (see NICE's guidance on boceprevir for the treatment of genotype 1 chronic hepatitis C and telaprevir for the treatment of genotype 1 chronic hepatitis C) are commonly used, and that for people with genotypes 1, 3 and 4 HCV, peginterferon alfa plus ribavirin is also used in clinical practice (see NICE's guidance on peginterferon alfa and ribavirin for the treatment of chronic hepatitis C, peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C and interferon alfa and ribavirin for the treatment of chronic hepatitis C). The clinical experts highlighted that some people with chronic

hepatitis C would choose not to have treatment with peginterferon alfa plus ribavirin because it can be associated with severe side effects, such as fatigue, neuropsychological effects and flu-like symptoms. The Committee also heard from the clinical experts that interferon-based treatment may cause chronic side effects that need additional long-term management and may therefore pose another barrier to people starting and completing treatment. Without treatment people risk further disease progression, for example, to compensated cirrhosis. The clinical experts commented that watchful waiting may be considered an appropriate option for some people. The clinical experts suggested that this option would be likely to become a less common choice in the era of interferon-free treatments, particularly because of the possibility that some people could be lost to follow-up. The Committee recognised the importance of having further treatment options available for people with chronic hepatitis C, and that an interferon-free treatment, such as ledipasvir–sofosbuvir, would provide a valuable treatment option.

4.3 The Committee discussed whether the technologies that had recently been granted a marketing authorisation for treating adults with chronic hepatitis C were established clinical practice in England. The Committee was aware that:

- For people with genotypes 1 and 4 chronic hepatitis C, whose disease has or has not been previously treated, NICE's guidance on simeprevir for treating chronic hepatitis C recommends simeprevir in combination with peginterferon alfa and ribavirin as an option.
- For people with genotypes 1 to 6 chronic hepatitis C, whose disease has or has not been previously treated, NICE's guidance on sofosbuvir for treating chronic hepatitis C

recommends sofosbuvir in combination with ribavirin, with or without peginterferon alfa, as an option for some people.

The patient expert commented that all current treatment options for people with genotype 1 and 4 HCV, including those recommended in NICE's guidance on sofosbuvir (given sofosbuvir plus ribavirin is not recommended for people with genotype 1 or 4 HCV) and on simeprevir, involve injecting interferon weekly. The Committee acknowledged that the marketing authorisation for ledipasvir–sofosbuvir offers people the option to have shortened courses of treatment, without peginterferon alfa, thereby avoiding the adverse effects associated with interferon-based therapy. The Committee was also aware that the oral combination of simeprevir plus sofosbuvir has not been appraised by NICE. Therefore it could not be considered as established practice. The Committee concluded that sofosbuvir in combination with ribavirin, with or without peginterferon alfa, and simeprevir in combination with peginterferon alfa and ribavirin, as recommended in NICE guidance, were relevant comparators for ledipasvir–sofosbuvir.

Clinical effectiveness

4.4 The Committee discussed the clinical-effectiveness evidence for ledipasvir–sofosbuvir in people with genotype 1 HCV. The Committee was aware that most people enrolled into the ION studies had genotype 1 HCV without cirrhosis, but that the sustained virological responses at 12 weeks (SVR12) for people with and without cirrhosis were similar, irrespective of treatment history (that is, treatment-naive or treatment-experienced HCV). The Committee noted that no head-to-head studies of ledipasvir–sofosbuvir with any of the comparators listed in the scope were available, and the ION studies used historical controls. The company highlighted that of the 1952 people enrolled into the 3

phase III ION studies, 96.7% were cured of HCV and only 1.8% had virologic relapse after treatment. The Committee heard from the clinical and patient experts that the results in people with genotype 1 HCV were impressive. The clinical experts stated that the SVR rates from the ledipasvir–sofosbuvir trials were generalisable to clinical practice. The Committee also heard from the clinical experts that people would be more likely to adhere to ledipasvir–sofosbuvir treatment than other currently available treatments, which is important to achieving an SVR, because it was shorter and interferon-free. The Committee highlighted the weaknesses associated with studies that used historical controls rather than a conventional control group, but concluded that the 3 phase III ION studies showed that ledipasvir–sofosbuvir was an effective treatment in people with genotype 1 HCV.

4.5 The Committee discussed the clinical-effectiveness evidence for ledipasvir–sofosbuvir in people with genotype 4 HCV. The Committee noted that there were limited data available in people with genotype 4 HCV. It agreed that this increased the uncertainty about whether the SVR rates from the genotype 4 HCV population would be seen in clinical practice. It also questioned whether the SVR rates for people with genotype 1 HCV could be generalised to people with genotype 4 HCV. The Committee acknowledged the company's view that people with genotypes 1 and 4 HCV have responded similarly to treatment in the past, and noted that the European Medicines Agency considered that the efficacy of ledipasvir–sofosbuvir for genotype 1 HCV in the ION studies were relevant to genotype 4 HCV. The Committee remained concerned about the lack of head-to-head trials, and the small numbers of people with genotype 4 HCV included in the evidence base. However, it concluded that it was satisfied that ledipasvir–sofosbuvir would potentially demonstrate a similar treatment effect

in people with genotype 4 HCV to that shown for people with genotype 1 HCV (with or without cirrhosis).

4.6 The Committee discussed the recommended treatment durations for ledipasvir–sofosbuvir in people with genotypes 1 and 4 HCV without cirrhosis. The Committee was aware that the marketing authorisation recommends durations of 8, 12 and 24 weeks of ledipasvir–sofosbuvir, depending on genotype, treatment history, risk of progression and cirrhosis status. It also recognised that the company had submitted a post-hoc analysis to identify people for whom 8 weeks of treatment would be appropriate (see section 3.7). These were people with genotype 1 whose HCV was treatment-naive, who do not have cirrhosis and who have a viral load of less than 6 million IU/ml. However, the Committee was aware that although the marketing authorisation did specify that people with genotype 1 whose HCV was treatment-naive were suitable for 8-weeks' treatment, the viral load criterion was not specified. The Committee noted that the populations defined by the European Medicines Agency for each treatment duration of ledipasvir–sofosbuvir recommended in the marketing authorisation were open to interpretation, and heard from the clinical experts that these groups were not clearly defined in clinical practice. The Committee heard from the company that the European Medicines Agency had taken a conservative approach by recommending longer treatment durations, because the ION studies did not show any additional harm (that is, a similar risk-benefit profile) from increasing the duration of treatment from 8 to 12 weeks, or from 12 to 24 weeks. The company commented further that increasing the treatment duration only 'marginally increased the SVR rates'. The clinical experts stated that overall, the SVR rates in the ION studies were impressive irrespective of treatment duration, and that in general people would prefer to have shorter treatments. The Committee

concluded that ledipasvir–sofosbuvir appeared similarly effective across the different durations used, and that it would make recommendations for each treatment duration separately in people with genotypes 1 and 4 HCV without cirrhosis.

4.7 The Committee discussed the recommended treatment durations for people with genotype 1 and 4 HCV with cirrhosis. The Committee noted that the marketing authorisation recommends 12 weeks of ledipasvir–sofosbuvir rather than 24 weeks of ledipasvir–sofosbuvir for these populations if the patient is 'deemed at low risk for clinical disease progression and has subsequent retreatment options'. The Committee heard from the company that it considered these criteria were vague and again, a consequence that there was no additional risk from extending the treatment duration of ledipasvir–sofosbuvir (see section 4.6). The clinical experts agreed it was very challenging to distinguish between high-risk and low-risk cirrhosis without any specific biomarkers, and the data from the ION studies showed benefits for 12-week treatment in most people. The clinical experts agreed with the patient expert that all people with cirrhosis would generally be considered as high risk, but that 12 weeks of ledipasvir–sofosbuvir offers major advantages over currently available treatment options, especially in populations with historically difficult-to-treat HCV. The Committee agreed that it was difficult to define 'low risk of clinical progression'. It concluded that it would make recommendations for each treatment duration separately in people with genotypes 1 and 4 HCV with cirrhosis.

4.8 The Committee discussed the clinical-effectiveness evidence for ledipasvir–sofosbuvir plus ribavirin in people with genotype 3 HCV. The Committee was aware that limited evidence was available for people with genotype 3 HCV, particularly for the treatment-naive HCV population (n=26). The Committee acknowledged that at the

time of the company's original submission (and as included in the company's economic model) data for sustained virological response at 4 weeks (SVR4) were only available for 50 people with treatment-experienced genotype 3 HCV. The Committee heard from the company that ELECTRON-2 was a phase II study, so small numbers of people were inevitable, but that SVR12 data were now available for the treatment-experienced population. These showed that only 1 of the 42 people who had an SVR4 did not have an SVR12. The Committee understood that people in ELECTRON-2 had 12 weeks of ledipasvir–sofosbuvir plus ribavirin, but the marketing authorisation recommends 24 weeks of treatment in people with cirrhosis or who had prior treatment. The company commented that the European Medicines Agency conservatively recommended a 24-week treatment because this was historically a population with difficult-to-treat HCV, and because of the limited trial data available. The Committee heard from the clinical experts that it was difficult to determine whether the SVR rates in ELECTRON-2 would be seen in clinical practice, because of the small patient numbers, but emphasised that the initial 12-week results were impressive, and they did not signal any safety issues from extending the treatment duration to 24 weeks. The Committee concluded that although there was uncertainty about the robustness of the evidence base in people with genotype 3 HCV, there was sufficient evidence for the Committee to consider ledipasvir–sofosbuvir plus ribavirin in people with genotype 3 HCV.

4.9 The Committee discussed the company's approach to estimating the relative effectiveness of ledipasvir–sofosbuvir (with or without ribavirin) compared with the comparators in the scope. The Committee noted that the company did not attempt a mixed treatment comparison because the ledipasvir–sofosbuvir trials were single arm. However it understood from the Evidence Review

Group (ERG) that it would have been possible to do a mixed treatment comparison for the comparators for genotype 1 HCV. The Committee commented that the company's naive indirect comparison approach was not robust and leads to considerable uncertainty in determining the size of the true treatment effect. The Committee understood from previous NICE technology appraisals that the SVR rates were likely to depend on the characteristics of the populations recruited into the studies, particularly for comparator therapies such as peginterferon alfa plus ribavirin, which may affect the relative treatment effect. The Committee was concerned that the company had selected SVR rates from single studies without justification, particularly because this uncertainty was not captured in the company's estimates of cost effectiveness. The Committee heard from the company that a network could not be formed for all technologies in the relevant populations because of data limitations. The company also stated that the cost-effectiveness results were not sensitive to the choice of SVR rates for the comparators used in its economic model. In addition, the company considered that because SVR is a hard end point, it did not consider its approach to increase uncertainty. However, the Committee heard from the ERG that the SVR rates of comparators did not need to change by much for potential conclusions around the cost effectiveness to change. The Committee concluded that the company's evidence for estimating the relative effectiveness of ledipasvir–sofosbuvir (with or without ribavirin) in people with genotypes 1, 3 and 4 HCV was not robust, and therefore this uncertainty should be taken into account in the decision-making.

Cost effectiveness

4.10 The Committee considered the company's economic model, the ERG's critique and the ERG's exploratory analyses. The Committee noted that the company's economic model structure

differed slightly from that used in previous NICE technology appraisals for hepatitis C. This was because people with mild and moderate chronic hepatitis C were grouped within a single health state, and therefore the company's model distinguished only between people with and without cirrhosis. However, the Committee heard from the company that its economic model structure was similar to that in NICE's guidance on sofosbuvir for treating chronic hepatitis C. The clinical experts considered that the model structure was consistent with how people are diagnosed in clinical practice. The Committee heard from the clinical experts that in the past invasive liver biopsies were used to diagnose mild, moderate or severe hepatitis C. However, current practice involves less invasive diagnostic tests that do not differentiate between mild and moderate disease and can distinguish only between cirrhosis and no cirrhosis. The Committee concluded that the approach taken by the company was appropriate.

4.11 The Committee discussed the company's weighted-average approach (or 'blended comparison'; see section 3.23). The Committee noted that the company's base-case analysis presented incremental cost-effectiveness ratios (ICERs) for a combined group of people with and without cirrhosis. The Committee was aware that cirrhosis affects the recommended regimen for ledipasvir–sofosbuvir and a person's likelihood of an SVR with comparator treatments, and therefore the cost effectiveness of treatment with ledipasvir–sofosbuvir. The Committee acknowledged that the patient numbers underpinning the clinical evidence used in the company's economic model were small for the groups of people with cirrhosis (including those with genotype 1 HCV), and that the SVR rates were relatively similar to those reported for ledipasvir–sofosbuvir in people without cirrhosis. However, the Committee concluded that it was appropriate to use the approach taken in the

ERG's exploratory analyses, in line with the marketing authorisation, which considered people with and without cirrhosis separately, and estimated the cost effectiveness of ledipasvir–sofosbuvir for each recommended treatment duration.

4.12 The Committee discussed the baseline characteristics of the population included in the company's economic model. The Committee noted that the ICERs were sensitive to the mean starting age used in the model. It was aware that the mean starting age was 40 years (for treatment-naive HCV) and 45 years (for treatment-experienced HCV) based on data from the HCV Research UK database, but the mean age of people in the ION studies was between 51 and 57 years. The Committee heard from the company that it chose to use the mean age from the HCV Research UK database because it more closely reflected the clinical population in England (and included a larger group of people) than the mean age of the population in the predominantly US-based ION studies. The Committee concluded that the mean age from the HCV Research UK database was more relevant to the clinical population in England.

4.13 The Committee discussed the transition probabilities used in the company's economic model. The Committee understood that the company had used transition probabilities for compensated or decompensated cirrhosis to hepatocellular carcinoma from Cardoso et al. (2010), which Gilead Sciences used in its revised economic model after the first consultation for NICE's guidance on sofosbuvir for treating chronic hepatitis C. The Committee noted that the ERG's exploratory analysis included transition probabilities for these health states from Fattovich et al. (1997), and was aware from the NICE guidance on sofosbuvir that although each source was associated with significant uncertainty they each had some face validity. The Committee considered that Cardoso et al. was an

acceptable source for transition probabilities, but that exploring alternative sources for transition probabilities, such as Fattovich et al., was also valuable because both values could be considered plausible. The Committee concluded that the transition probabilities may lie somewhere between the Cardoso et al. and Fattovich et al. estimates, and therefore both sources should be taken into account in the decision-making.

4.14 The Committee discussed the utility values used in the company's model. The Committee acknowledged that health-related quality of life was assessed in the ION studies using the SF-36 questionnaire and that none of the clinical trials collected data using the EQ-5D. The Committee noted that the company had therefore included a utility benefit of 0.04 for people who had an SVR, taken from Vera-Llonch et al. (2013). It noted that this was estimated with the US EQ-5D tariff, rather than the UK EQ-5D tariff (Wright et al. 2006, which estimated a utility benefit of 0.05). The Committee heard from the company that it chose Vera-Llonch et al. for the utility benefit estimate because this was the most recent source used in its economic model for the NICE guidance on sofosbuvir for treating chronic hepatitis C. The Committee was aware that the ERG's exploratory analysis showed that the ICERs reduced slightly in favour of ledipasvir–sofosbuvir when using the utility benefit from Wright et al. However, it also noted further analyses by the ERG that removed a utility benefit after an SVR substantially increased the ICERs associated with ledipasvir–sofosbuvir. The company stated that it was unable to include utility estimates from the ION studies because data were not available at the time of its evidence submission. The Committee agreed that the health-related quality-of-life data available from the ION studies suggested some benefit with ledipasvir–sofosbuvir, but the results were not consistent across the 3 phase III studies and the 4 questionnaires assessed

so it was difficult to approximate how much benefit people were likely to gain. In addition, the Committee was concerned that the utility accrued over a person's lifetime in the company's model was likely to be overestimated because the utility values were not adjusted for increasing age, and therefore, the utility benefit from an SVR was assumed to be maintained until death. The Committee concluded that it would have preferred to have seen the utility values determined directly from the ION studies and to have the utility values in the model adjusted for increasing age, but it was prepared to accept the utility benefit from Vera-Llonch et al.

4.15 The Committee discussed whether it was appropriate to exclude the health effects from reinfection and onward transmission in the analysis. The Committee noted that excluding reinfection may overestimate the health benefits of more effective treatments and underestimate their costs, because people would be retreated with other therapies in clinical practice. The Committee understood from the clinical experts that the rate of reinfection was relatively small (approximately 1%). However, the Committee also acknowledged that most people who do not have an SVR after treatment were also likely to have further treatment in clinical practice (including people whose HCV relapses after having an initial SVR), and this too had not been accounted for in the company's economic model. The Committee recognised that excluding onward transmission may underestimate the health benefits of more effective treatments. The Committee commented that the ICERs were associated with some uncertainty because these health effects were omitted. It would have preferred the company to explore their inclusion further, but appreciated that this would have needed a different (and potentially more complex) model structure. The Committee concluded that ICERs excluding the health effects of reinfection

and onward transmission were acceptable to use but this uncertainty should be taken into account in the decision-making.

4.16 The Committee acknowledged that all the ICERs presented depended on the clinical-effectiveness data, which was associated with considerable uncertainty, namely:

- the clinical study designs (these were open-label, non-randomised controlled evidence, with no head-to-head studies)
- the selection of SVR rates for comparators from single studies (given that patient and clinical characteristics influence SVR rates for each treatment differently and within each HCV genotype, and the sensitivity of the ICERs to the choice of SVR rates as shown in the ERG's exploratory threshold analysis)
- the use of an uncontrolled naive indirect comparison to estimate the relative effectiveness of ledipasvir–sofosbuvir and its comparators.

The Committee heard from the clinical experts that in clinical practice most people who do not have an SVR after a course of treatment are likely to have further treatment. The Committee noted that for all the ICERs presented, retreatment was not accounted for and it was uncertain whether this was likely to increase or decrease the cost effectiveness of ledipasvir–sofosbuvir. The Committee concluded that all ICERs presented are associated with considerable uncertainty.

Genotypes 1 and 4

Treatment-naive HCV without cirrhosis

4.17 The Committee discussed the ICERs for ledipasvir–sofosbuvir in people with treatment-naive, genotype 1 HCV without cirrhosis. The Committee reiterated the uncertainties associated with the clinical evidence included in the economic modelling (see section 4.16).

The Committee highlighted that the ERG's base-case incremental ICERs for 8 weeks and 12 weeks of ledipasvir–sofosbuvir in people with treatment-naive, genotype 1 HCV without cirrhosis were £9000 (compared with peginterferon alfa plus ribavirin) and £23,000 (compared with simeprevir plus peginterferon alfa and ribavirin) per quality-adjusted life year (QALY) gained respectively. The Committee inferred that the ERG's ICERs increased by approximately £3000 per QALY gained when using the transition probabilities from Fattovich et al. 1997 rather than from Cardoso et al. 2010 (see table 11). On balance, the Committee was of the view that the ICERs for ledipasvir–sofosbuvir may increase if the company had accounted for the additional uncertainty associated with the clinical- and cost-effectiveness evidence. The Committee concluded that 12 weeks of ledipasvir–sofosbuvir could not be considered a cost-effective use of NHS resources in this population. The Committee concluded that 8 weeks of ledipasvir–sofosbuvir could be considered a cost-effective use of NHS resources for people with treatment-naive, genotype 1 HCV without cirrhosis.

4.18 The Committee discussed the ICERs for ledipasvir–sofosbuvir in people with treatment-naive genotype 4 HCV without cirrhosis. It noted that the marketing authorisation for ledipasvir–sofosbuvir does not recommend the 8-week treatment for the genotype 4 HCV population, and therefore it could not make a recommendation for this treatment duration in people with genotype 4 HCV. The Committee reiterated the uncertainties associated with the clinical evidence included in the economic modelling (see section 4.16), and noted the specific uncertainty about the small patient numbers for the data available in people with genotype 4 HCV (see section 4.5). The Committee noted further uncertainty in the relative effectiveness estimates for this population because the SVR rates

for the comparators in people with genotype 4 HCV were based on people with genotype 1 HCV, which may not be representative. However, it agreed that it would consider the ICERs presented for people with genotype 4 HCV that used data from people with genotype 1 HCV (that is, the ICERs available for people with genotype 4 HCV were the same as those estimated for people with genotype 1 HCV). The Committee highlighted its conclusions for 12 weeks of ledipasvir–sofosbuvir in people with treatment-naive, genotype 1 HCV without cirrhosis (see section 4.17), and concluded that it could not consider 12 weeks of ledipasvir–sofosbuvir in people with treatment-naive, genotype 4 HCV without cirrhosis to be a cost-effective use of NHS resources.

Treatment-naive HCV with cirrhosis

4.19 The Committee discussed the ICERs for ledipasvir–sofosbuvir in people with treatment-naive genotype 1 or 4 HCV with cirrhosis. The Committee noted that the marketing authorisation for ledipasvir–sofosbuvir recommends different treatment durations for people with high-risk and low-risk cirrhosis. However, it heard from the company and clinical experts that it was challenging to distinguish between these groups in clinical practice (see section 4.7). The Committee recognised that a similar quality of evidence had been presented for the 12-week and 24-week treatments for the genotype 1 HCV population from the ION studies, which showed relatively similar SVR rates and risk of relapse between the treatment durations. However, the Committee highlighted that the data available for people with cirrhosis from the ION studies were based on small patient numbers. It further reiterated the other uncertainties associated with the evidence (see sections 4.16 and 4.18). The Committee highlighted that the ERG's incremental ICERs for ledipasvir–sofosbuvir in people with treatment-naive genotype 1 or 4 HCV with cirrhosis were £5000

(12 weeks of treatment, compared with no treatment) and £45,000 (24 weeks of treatment, compared with sofosbuvir plus peginterferon alfa and ribavirin) per QALY gained. The Committee understood that the ERG's ICERs for this population were highly sensitive to the evidence source used for transition probabilities, and that they increased approximately 2-fold when using the transition probabilities from Fattovich et al. 1997 rather than from Cardoso et al. 2010 (see table 11). On balance, the Committee concluded that only 12-week ledipasvir–sofosbuvir treatment could be considered a cost-effective use of NHS resources in people with treatment-naive genotype 1 or 4 HCV with cirrhosis.

Treatment-experienced HCV without cirrhosis

4.20 The Committee discussed the ICERs for ledipasvir–sofosbuvir in people with treatment-experienced genotype 1 or 4 HCV without cirrhosis. It reiterated the uncertainties associated with the evidence (see sections 4.16 and 4.18). The Committee highlighted that the ERG's incremental ICERs for ledipasvir–sofosbuvir in people with treatment-experienced genotype 1 or 4 HCV without cirrhosis were £17,000 (12 weeks of treatment, compared with no treatment) and £77,500 (24 weeks of treatment, compared with simeprevir plus peginterferon alfa and ribavirin) per QALY gained. The Committee noted that the ERG's ICER for 12-week treatment increased by approximately £2000 per QALY gained when using the transition probabilities from Fattovich et al. 1997 rather than from Cardoso et al. 2010 (see table 11). On balance, the Committee concluded that only 12-week ledipasvir–sofosbuvir treatment could be considered a cost-effective use of NHS resources in people with treatment-experienced genotype 1 or 4 HCV without cirrhosis.

Treatment-experienced HCV with cirrhosis

4.21 The Committee discussed the ICERs for ledipasvir–sofosbuvir in people with treatment-experienced genotype 1 or 4 HCV with cirrhosis. It reiterated the uncertainties associated with the evidence (see sections 4.16, 4.18 and 4.19). The Committee was aware it had been presented with ICERs from the ERG in people having the 24-week treatment only because the marketing authorisation states that 12 weeks' treatment "may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options". Therefore, the Committee agreed that the marketing authorisation does not recommend 12 weeks of treatment for people with treatment-experienced genotype 1 or 4 HCV with cirrhosis, and considered therefore it could not make a recommendation for 12 weeks' of treatment. The Committee noted that the ERG's ICER for 24 weeks of ledipasvir–sofosbuvir in people with treatment-experienced genotype 1 or 4 HCV with cirrhosis was £32,500 per QALY gained (compared with sofosbuvir plus peginterferon alfa and ribavirin). The Committee understood that the ERG's ICERs for this population were highly sensitive to the evidence source used for transition probabilities, and that they increased approximately 2-fold when using the transition probabilities from Fattovich et al. 1997 rather than from Cardoso et al. 2010 (see table 11). The Committee concluded that 24-week ledipasvir–sofosbuvir treatment could not be considered a cost-effective use of NHS resources in people with treatment-experienced genotype 1 or 4 HCV with cirrhosis.

Genotype 3

4.22 The Committee discussed the ICERs for ledipasvir–sofosbuvir plus ribavirin in people with genotype 3 HCV. The Committee noted that the marketing authorisation only recommends a treatment duration (24 weeks) for people with cirrhosis or people who have had

treatment before in the genotype 3 HCV population, but not for treatment-naive HCV and people who do not have cirrhosis. The Committee agreed with the company that 12 weeks of ledipasvir–sofosbuvir plus ribavirin was included in the marketing authorisation for treatment-naive, genotype 3 HCV without cirrhosis. The Committee emphasised their concerns about the robustness of the evidence base in people with genotype 3 HCV (see section 4.8), and recognised that the uncertainties in the methods used to estimate the relative effectiveness, and the uncertainty of excluding further treatment in the economic modelling, still applied to its decision-making for people with genotype 3 HCV. The Committee noted that all the ICERs presented for those with treatment-naive genotype 3 HCV without cirrhosis (12-weeks' treatment) or with cirrhosis (24-weeks' treatment), and for treatment-experienced genotype 3 HCV without cirrhosis (24-weeks' treatment), were over £30,000 per QALY gained (see tables 11 and 12). However, it noted that the ERG had also presented ICERs for treatment-experienced, genotype 3 HCV with cirrhosis when interferon was not suitable (see section 3.20). The Committee noted that for the treatment-experienced, genotype 3 HCV group with cirrhosis for whom interferon is unsuitable, the ERG's incremental ICER was £18,000 per QALY gained for 24 weeks of ledipasvir–sofosbuvir plus ribavirin compared with no treatment. The Committee was aware that this ICER increased from £18,000 to £30,500 per QALY gained when using the transition probabilities from Fattovich et al. 1997 rather than from Cardoso et al. 2010 (see table 11). On balance, the Committee agreed that the ICER for ledipasvir–sofosbuvir plus ribavirin in people with treatment-experienced genotype 3 HCV with cirrhosis for whom interferon therapy is unsuitable, may increase if the company had accounted for the additional uncertainty associated with the clinical- and cost-effectiveness evidence. The Committee agreed that recommending

ledipasvir-sofosbuvir plus ribavirin for people with treatment-experienced genotype 3 HCV with cirrhosis for whom interferon therapy is unsuitable would therefore represent an inefficient use of NHS resources. The Committee concluded that ledipasvir-sofosbuvir plus ribavirin could not be considered a cost-effective use of NHS resources in people with genotype 3 HCV.

People co-infected with HIV

4.23 The Committee discussed whether the evidence submitted by the company allowed it to make recommendations for people co-infected with HIV. It noted that the clinical-effectiveness evidence presented in the company's submission was from a single-centre, open-label, ongoing phase II study in adults with treatment-naive genotype 1 HCV, co-infected with HIV and without cirrhosis. The Committee acknowledged that the interim results of this study suggested that the SVR12 in people with HCV and HIV co-infection was similar to that seen in people with HCV mono-infection. The Committee was aware that the company had not submitted cost-effectiveness estimates for people co-infected with HIV and that the company considered this to be conservative because people with HCV who are co-infected with HIV are likely to progress to severe health states more quickly if left untreated than people with HCV mono-infection. The company stated that therefore ledipasvir–sofosbuvir was more likely to be cost effective in this population. However, the Committee noted that this assumption did not acknowledge other causes of mortality that were also likely to influence the cost-effectiveness results. The Committee understood that the ledipasvir–sofosbuvir summary of product characteristics states that people with HCV and HIV co-infection should have the same treatment regimen as people with HCV mono-infection. On balance, the Committee concluded that it was reasonable to extend the recommendations made for the mono-infected group to those

co-infected with HCV and HIV. However, the Committee agreed that future modelling and economic analyses should be presented separately for this population.

People with advanced liver disease and after liver transplant

4.24 The Committee discussed whether the evidence submitted by the company allowed it make recommendations for people with advanced liver disease and after liver transplant. The Committee highlighted that the marketing authorisation for ledipasvir–sofosbuvir recommends only 24 weeks of treatment plus ribavirin in people with advanced liver disease and after liver transplant. It noted that the company submitted clinical-effectiveness evidence using SVR4 data from 1 multicentre open-label, phase II non-randomised controlled trial in adults with genotype 1 or 4 HCV, but had not explored the cost effectiveness of 24 weeks of ledipasvir–sofosbuvir plus ribavirin in people with advanced liver disease and after liver transplant. The Committee was aware that the company estimated the cost-effectiveness in this population before NHS England had commissioned its use. The Committee heard from the company that it had not presented these estimates in its evidence submission because they were based on a simplified assumption that within 1 year all people with compensated cirrhosis have decompensated cirrhosis, and were not based on evidence. The Committee noted that the ICERs in the ERG's exploratory analyses, which explored the use of 24 weeks' ledipasvir–sofosbuvir (with or without ribavirin and across all HCV genotypes, see sections 4.19-20 and 4.22), were substantially higher than the range that could be considered a cost-effective use of NHS resources. On balance, the Committee concluded that without cost-effectiveness estimates it was unable to make recommendations for ledipasvir–sofosbuvir plus ribavirin in people with advanced liver disease and after liver transplant.

4.25 The Committee discussed whether ledipasvir–sofosbuvir could be considered innovative, and whether the company's economic analysis had captured all changes in health-related quality of life. The Committee agreed that ledipasvir–sofosbuvir offers oral, shortened, and interferon-free treatments, which are particularly important to people, and a major development in the clinical management of chronic hepatitis C. The Committee therefore acknowledged that ledipasvir–sofosbuvir is a valuable new therapy for treating chronic hepatitis C. The Committee agreed that there were other benefits for people with hepatitis C (for example, the potential for regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV; see section 4.15) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs.

4.26 The Committee noted the potential equality issue raised by the company that minority ethnic groups and people with HIV co-infection are more highly represented in the genotype 4 HCV population than in the genotype 1 or 3 populations. In light of NICE's legal obligation to promote equality, the Committee considered the evidence provided by the company that included family origin by HCV genotype, and the prevalence of HIV and HCV co-infection (see section 3.56). The Committee noted that the family origin evidence was self-reported (and therefore could not be verified), and used broad categories. The Committee therefore considered this evidence to be uncertain, but acknowledged that the data had been published by Public Health England. The Committee acknowledged that the proportion of people in Europe with genotype 4 HCV was low, and the company was carrying out several studies of ledipasvir–sofosbuvir in people with genotype 4 HCV. The Committee considered the commercial-in-confidence evidence presented by the company about the genotype

distribution of HCV in people with HCV and HIV co-infection and agreed that a disproportionate number of people had genotype 4 HCV and HIV co-infection compared with the overall population of people with HCV in England. The Committee was satisfied that it had sufficiently considered the evidence available for people with genotype 4 HCV, which was limited. With no mature data available, the Committee had attempted to bridge this evidence gap by considering whether the evidence available for genotype 1 HCV was generalisable to the genotype 4 HCV population, and based on the cost effectiveness data had made recommendations that were aligned with the treatment duration and ribavirin co-administration stated in the marketing authorisation. Therefore, the Committee agreed that its recommendations were fair and did not constitute an equality issue.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Ledipasvir–sofosbuvir for treating chronic hepatitis C	Section
Key conclusion		
The Committee acknowledged that all the ICERs presented depended on the clinical-effectiveness data, which was associated with considerable uncertainty, namely: • the clinical study designs (open-label, non-randomised controlled evidence, with no head-to-head studies) • the selection of SVR rates for comparators from single studies • the use of an uncontrolled naive indirect comparison to estimate the relative effectiveness.		4.16
Treatment-naive genotype 1 HCV without cirrhosis The Committee highlighted that the ERG's base-case incremental ICERs for 8 weeks and 12 weeks of ledipasvir–sofosbuvir in people with treatment-naive, genotype 1 HCV without cirrhosis were £9000 (compared with peginterferon alfa plus ribavirin) and £23,000 (compared with simeprevir plus peginterferon alfa and ribavirin) per QALY gained respectively. The Committee concluded that, even allowing for a potential relapse rate of approximately 10%, 8 weeks of ledipasvir–sofosbuvir could be considered a cost-effective use of NHS resources for people with treatment-naive,		4.17

genotype 1 HCV without cirrhosis. The Committee concluded that 12 weeks of ledipasvir–sofosbuvir could not be considered a cost-effective use of NHS resources in this population.	
Treatment-naive genotype 4 HCV without cirrhosis The Committee agreed that it would consider the ICERs presented for people with genotype 4 HCV that used data from people with genotype 1 HCV. The Committee highlighted its conclusions for 12 weeks of ledipasvir–sofosbuvir in people with treatment-naive, genotype 1 HCV without cirrhosis, and concluded that it could not consider 12 weeks of ledipasvir–sofosbuvir in people with treatment-naive, genotype 4 HCV without cirrhosis to be a cost-effective use of NHS resources.	4.18
Treatment-naive genotype 1 or 4 HCV with cirrhosis The Committee highlighted that the ERG's incremental ICERs for ledipasvir–sofosbuvir in people with treatment-naive genotype 1 or 4 HCV with cirrhosis were £5000 (12 weeks of treatment, compared with no treatment) and £45,000 (24 weeks of treatment, compared with sofosbuvir plus peginterferon alfa and ribavirin) per QALY gained. On balance, the Committee concluded that only 12-week ledipasvir–sofosbuvir treatment could be considered a cost-effective use of NHS resources in people with treatment-naive genotype 1 or 4 HCV with cirrhosis.	4.19
Treatment-experienced genotype 1 or 4 HCV without cirrhosis The Committee highlighted that the ERG's incremental ICERs for ledipasvir–sofosbuvir in people with treatment-experienced genotype 1 or 4 HCV without cirrhosis were £17,000 (12 weeks of treatment, compared with no treatment) and £77,500 (24 weeks of treatment, compared with simeprevir plus peginterferon alfa and ribavirin) per QALY gained. On balance, the Committee concluded that only 12-week ledipasvir–sofosbuvir treatment could be considered a cost-effective use of NHS resources in people with treatment-experienced genotype 1 or 4 HCV without cirrhosis.	4.20
Treatment-experienced genotype 1 or 4 HCV with cirrhosis The Committee noted that the ERG's ICER for 24 weeks of ledipasvir–sofosbuvir in people with treatment-experienced genotype 1 or 4 HCV with cirrhosis was £32,500 per QALY gained (compared with sofosbuvir plus peginterferon alfa and ribavirin). The Committee concluded that 24-week ledipasvir–sofosbuvir treatment could not be considered a cost-effective use of NHS resources in people with treatment-experienced genotype 1 or 4 HCV with cirrhosis.	4.21
Genotype 3 HCV The Committee emphasised their concerns about the robustness of the evidence base in people with genotype 3 HCV, and recognised that the uncertainties in the methods used to estimate the relative effectiveness still	4.22

applied to its decision-making for people with genotype 3 HCV. The Committee noted that all the ICERs presented for those with treatment-naive genotype 3 HCV with or without cirrhosis were over £30,000 per QALY gained. It noted that the ICERs for people with treatment-experienced, genotype 3 HCV and cirrhosis for whom interferon was not suitable ranged from £18,000 to £30,500 per QALY gained for 24 weeks of ledipasvir–sofosbuvir plus ribavirin (compared with no treatment), and agreed this may increase when accounting for the additional uncertainty associated with the evidence. The Committee agreed that recommending ledipasvir-sofosbuvir plus ribavirin for people with treatment-experienced genotype 3 HCV with cirrhosis for whom interferon therapy is unsuitable would therefore represent an inefficient use of NHS resources. The Committee concluded that ledipasvir-sofosbuvir plus ribavirin could not be considered a cost-effective use of NHS resources in people with genotype 3 HCV.	
People co-infected with HIV The Committee acknowledged that the company's interim results suggested that the SVR12 in people with HCV and HIV co-infection was similar to that seen in people with HCV mono-infection. The Committee concluded that it was reasonable to extend the recommendations made for the mono-infected group to those co-infected with HCV and HIV.	4.23
People with advanced liver disease and after liver transplant The Committee highlighted that the marketing authorisation for ledipasvir–sofosbuvir recommends only 24 weeks of treatment plus ribavirin in people with advanced liver disease and after liver transplant, which the company had not explored in its cost effectiveness analysis. The Committee concluded that without cost-effectiveness estimates it was unable to make recommendations for ledipasvir–sofosbuvir plus ribavirin in people with advanced liver disease and after liver transplant.	4.24

Current practice		
Clinical need of patients, including the availability of alternative treatments	Treatment decisions and response to treatment are influenced by HCV genotype, level of liver damage, comorbidities and treatment history. For people with genotype 1 HCV, the Committee heard that boceprevir plus peginterferon alfa and ribavirin or telaprevir plus peginterferon alfa and ribavirin are commonly used, and that for people with genotypes 1, 3 and 4 HCV, peginterferon alfa plus ribavirin is also used in clinical practice. The Committee concluded that sofosbuvir and simeprevir, as recommended in NICE guidance, were relevant comparators.	4.2 4.2 4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee agreed that ledipasvir–sofosbuvir offers oral, shortened, and interferon-free treatments, which is particularly important to people, and a major development in the clinical management of chronic hepatitis C.	4.25
What is the position of the treatment in the pathway of care for the condition?	The Committee recognised the importance of having further treatment options available for people with chronic hepatitis C, and that an interferon-free treatment, such as ledipasvir–sofosbuvir, would provide a valuable treatment option.	4.2
Adverse reactions	The Committee acknowledged that ledipasvir–sofosbuvir offers people the option to have shortened courses of treatment, without peginterferon alfa, thereby avoiding the adverse effects associated with interferon-based therapy.	3.17, 4.3
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee was aware that most people enrolled into the ION studies had genotype 1 HCV without cirrhosis. The Committee noted that no head-to-head studies of ledipasvir–sofosbuvir with any of the comparators listed in the scope were available, and the ION studies used historical controls.	4.4

	The Committee noted that there were limited data available in people with genotype 4 HCV. The Committee was aware that limited evidence was available for people with genotype 3 HCV, particularly for the treatment-naive HCV population.	4.5 4.8
Relevance to general clinical practice in the NHS	The clinical experts stated that the SVR rates from the ledipasvir–sofosbuvir trials were generalisable to clinical practice. The Committee noted that the populations defined by the EMA for each of the treatments were open to interpretation, and heard that these groups were not clearly defined in clinical practice.	4.4 4.6
Uncertainties generated by the evidence	The Committee acknowledged the company's view that people with genotypes 1 and 4 HCV have responded similarly to treatment in the past, and noted that the European Medicines Agency considered that the treatments for genotype 1 HCV in the ION studies were relevant to genotype 4 HCV. The Committee remained concerned about the lack of head-to-head trials, and the small numbers of people with genotype 4 HCV included in the evidence base. The Committee heard from the clinical experts that it was difficult to determine whether the SVR rates in ELECTRON-2 (genotype 3 HCV) would be seen in clinical practice, because of the small patient numbers, but emphasised that the initial 12-week results were impressive. The Committee commented that the company's naive indirect comparison approach was not robust and leads to considerably uncertainty in determining the size of the true treatment effect. The Committee was concerned that the company had selected SVR rates from single studies without justification.	4.5 4.8 4.9 4.9

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Genotype 1 HCV: Sustained virological responses at 12 weeks in people with and without cirrhosis were similar, irrespective of treatment history (that is, treatment-naive or treatment-experienced HCV).	4.4
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The company highlighted that of the 1952 people enrolled into the 3 phase III ION studies, 96.7% were cured of their HCV and only 1.8% had virologic relapse after treatment. The Committee highlighted the flaws associated with studies that used historical controls rather than a conventional control group, but concluded that the 3 phase III ION studies showed that ledipasvir–sofosbuvir was an effective treatment in people with genotype 1 HCV. The Committee concluded that it was satisfied that ledipasvir–sofosbuvir would potentially demonstrate a similar treatment effect in people with genotype 4 HCV to that shown for people with genotype 1 HCV (with or without cirrhosis). The Committee concluded that the company's evidence for estimating the relative effectiveness of ledipasvir–sofosbuvir (with or without ribavirin) in people with genotypes 1, 3 and 4 HCV was not robust, and therefore this uncertainty should be taken into account in the decision-making.	4.4 4.5 4.9
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the company's economic model, the ERG's critique and the ERG's exploratory analyses.	4.10

Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the company's base-case analysis presented incremental cost-effectiveness ratios (ICERs) for a combined group of people with and without cirrhosis. The Committee concluded that the transition probabilities for compensated or decompensated cirrhosis to hepatocellular carcinoma may lie somewhere between the Cardoso et al. and Fattovich et al. estimates. The company's utility benefit for SVR was estimated with the US EQ-5D tariff, rather than the UK EQ-5D tariff. The Committee agreed that the health-related quality-of-life data available from the ION studies suggested some benefit with ledipasvir–sofosbuvir, but the results were not consistent so it was difficult to approximate how much benefit people were likely to gain. In addition, the Committee was concerned that the utility accrued over a person's lifetime was likely to be overestimated because the utility values were not adjusted for increasing age. The Committee commented that the ICERs were associated with some uncertainty because health effects of reinfection and onward transmission were omitted. The Committee noted that retreatment was not accounted for and it was uncertain whether this was likely to increase or decrease the cost effectiveness of ledipasvir–sofosbuvir.	4.11 4.13 4.14 4.15 4.16
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee acknowledged that none of the clinical trials collected data using the EQ-5D. The Committee noted that the company had therefore included a utility benefit of 0.04 for people who had an SVR, taken from Vera-Llonch et al. The Committee agreed that there were other benefits for people with hepatitis C (for example, the potential for regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs.	4.14 4.25

Are there specific groups of people for whom the technology is particularly cost effective?	Please refer to the key conclusions above	
What are the key drivers of cost effectiveness?	The one-way sensitivity analyses showed that the company's ICERs were most sensitive to changes to the 'on-treatment' costs, discount rates of costs and effects, the SVR rates of ledipasvir–sofosbuvir and the comparators, and the transition probability from the non-cirrhotic to the compensated cirrhosis health state. The ERG concluded that using cost-effectiveness results dependent on the company's weighted-average approach (combining people with and without cirrhosis) may result in the recommendation of some options that represent an inefficient use of NHS resources.	3.28 3.50
Most likely cost-effectiveness estimate (given as an ICER)	Please refer to the key conclusions above	-
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	-
End-of-life considerations	Not applicable	-
Equalities considerations and social value judgements	The Committee noted the potential equality issue raised by the company that minority ethnic groups and people with HIV co-infection are more highly represented in the genotype 4 HCV population than in the genotype 1 or 3 populations. With no mature data available for people with genotype 4 HCV, the Committee had attempted to bridge this evidence gap by considering whether the evidence available for genotype 1 HCV was generalisable to the genotype 4 HCV population. Therefore, the Committee agreed that its recommendations were fair and did not constitute an equality issue.	4.26

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social

Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication. Although an extension to the deferred funding period was granted for NICE's guidance on sofosbuvir for treating chronic hepatitis C TA330 (until 31 July 2015; because the health technology cannot be appropriately administered until 'certain health service infrastructure requirements including goods, materials or other facilities, or other appropriate health services resources, including staff are in place'), it is not considered appropriate to extend the deferred funding period for this appraisal. The arrangements previously presented by NHS England in relation to TA330 are expected to have been implemented before it has to comply with NICE's final recommendations for ledipasvir-sofosbuvir.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has chronic hepatitis C and the doctor responsible for their care thinks that ledipasvir–sofosbuvir is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.

- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Simeprevir for treating genotype 1 or 4 chronic hepatitis C. NICE technology appraisal guidance 331 (2015).
- Sofosbuvir for treating chronic hepatitis C. NICE technology appraisal guidance 330 (2015).
- Needle and syringe programmes. NICE public health guidance 52 (2014).
- Boceprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 253 (2012).
- Telaprevir for the treatment of genotype 1 chronic hepatitis C. NICE technology appraisal guidance 252 (2012).
- Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 200 (2010).
- Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. NICE technology appraisal guidance 106 (2006).
- Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. NICE technology appraisal guidance 75 (2004).

Under development

- Daclatasvir for treating chronic hepatitis C. NICE technology appraisal. Publication expected August 2015.

- Ombitasvir/paritaprevir/ritonavir with or without dasabuvir for treating chronic hepatitis C. NICE technology appraisal. Publication expected September 2015.
- Hepatitis C: diagnosis and management of hepatitis C. NICE clinical guideline. Publication date to be confirmed.

NICE pathways

There is a NICE pathway on hepatitis B and C testing.

7 Proposed date for review of guidance

7.1 Several new treatments for chronic hepatitis C are being granted a marketing authorisation in the UK. According to clinical experts the approach to treating hepatitis C is likely to change rapidly next year because of the new technologies becoming available. The guidance on this technology will be considered for review within 1 year of publication, when other published guidance for hepatitis C is also reviewed. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, Appraisal Committee
February 2015

8 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
GP, West Coker Surgery, Somerset

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser

Dr Matthew Bradley
Therapy Area Leader, Global Health Outcomes, GlaxoSmithKline

Dr Ian Campbell

Honorary Consultant Physician, Llandough Hospital, Cardiff

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Mrs Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Professor John Hutton

Professor of Health Economics, University of York

Professor Steven Julious

Professor in Medical Statistics, University of Sheffield

Dr Malcolm Oswald

Lay Member

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Martyn Burke

Technical Lead

Dr Melinda Goodall

Technical Adviser

Kate Moore

Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR), The University of Sheffield:

- Thokala P, et al. Ledipasvir–sofosbuvir for treating chronic hepatitis C: A Single Technology Appraisal, January 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Giliead Sciences

II. Professional/expert and patient/carer groups:

- Haemophilia Society
- Hepatitis C Trust
- HIV i-Base
- Liver4Life
- Positively UK
- British Association for the Study of the Liver
- British HIV Association
- British Society of Gastroenterology
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Janssen (simeprevir, telaprevir)
- Merck Sharp & Dohme (boceprevir, peginterferon alfa 2b, ribavirin)
- Roche Products (peginterferon alfa 2a, ribavirin)
- Foundation for Liver Research
- School of Health and Related Research (ScHARR)
- National Institute for Health Research Health Technology Assessment Programme
- Public Health England

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on ledipasvir–sofosbuvir by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Matthew Cramp, Consultant Hepatologist, nominated by Gilead – clinical expert
- Dr Helen Harris, Clinical Scientist and Research Associate, nominated by Public Health England – clinical expert
- Mr Charles Gore, Chief Executive of the Hepatitis C Trust, nominated by the Hepatitis C Trust – patient expert
- Mr Richard Hall, Co-Founder of Liver4Life, nominated by Liver4Life – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Gilead Sciences