NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Sofosbuvir-velpatasvir 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 sofosbuvir-velpatasvir 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, 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 recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see 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 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 sofosbuvir-velpatasvir in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 14 October 2016

Second appraisal committee meeting: 26 October 2016

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 Sofosbuvir-velpatasvir is recommended as an option for treating chronic hepatitis C in adults, as specified in table 1, only if the company provides the drug with the discount agreed in the simple discount agreement.

Table 1 Sofosbuvir-velpatasvir for treating adults with chronic hepatitis C

HCV genotype	Liver disease stage	Treatment	Recommendation according to treatment history	
			Untreated	**Treated**
1	With or without compensated cirrhosis	Sofosbuvir-velpatasvir	Recommended	
2	Without cirrhosis	Sofosbuvir-velpatasvir	Recommended only for people who cannot tolerate interferon or it is not suitable for them	Recommended
	Compensated cirrhosis	Sofosbuvir-velpatasvir	Recommended	
3	Without cirrhosis	Sofosbuvir-velpatasvir	Recommended	
	Compensated cirrhosis	Sofosbuvir-velpatasvir (with or without ribavirin)	Recommended	
4	With or without compensated cirrhosis	Sofosbuvir-velpatasvir	Recommended	
5	With or without compensated cirrhosis	Sofosbuvir-velpatasvir	Recommended	
6	With or without compensated cirrhosis	Sofosbuvir-velpatasvir	Recommended	
1–6	Decompensated cirrhosis	Sofosbuvir-velpatasvir (with ribavirin)	Recommended	

Abbreviation: HCV, hepatitis C virus

Treated – the person's hepatitis C has not adequately responded to interferon−based treatment.

1.2 It is recommended that the decision to treat and prescribing decisions are made by multidisciplinary teams in the operational delivery networks put in place by NHS England, to prioritise treatment for people with the highest unmet clinical need.

1.3 This guidance is not intended to affect the position of patients whose treatment with sofosbuvir-velpatasvir was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Sofosbuvir-velpatasvir (Epclusa, Gilead) is a fixed-dose combination drug. Sofosbuvir inhibits hepatitis C virus (HCV) non-structural viral protein NS5B ribonucleic acid (RNA)-dependent RNA polymerase. Velpatasvir inhibits HCV non-structural protein NS5A.
Marketing authorisation	Sofosbuvir-velpatasvir has a marketing authorisation in the UK for treating chronic hepatitis C virus (HCV) infection in adults. Includes genotypes 1–6 HCV in people with or without compensated or decompensated cirrhosis.
Adverse reactions	The summary of product characteristics states that headache, fatigue and nausea are the most common adverse reactions (incidence of 10% or more). For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Sofosbuvir-velpatasvir is taken orally. The recommended dose is 1 tablet once daily, for 12 weeks. Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir. The marketing authorisation states that decompensated cirrhosis should be treated with sofosbuvir-velpatasvir in combination with ribavirin, for 12 weeks. Ribavirin plus sofosbuvir-velpatasvir may also be considered for people with genotype 3 HCV who have compensated cirrhosis.
Price	Sofosbuvir-velpatasvir costs £12,993.33 per 28-day pack. The total cost of a 12-week treatment course is £38,980. Ribavirin costs £246.65 per 56-tablet pack. The total cost of a 12-week treatment course of sofosbuvir-velpatasvir with ribavirin is £40,089.93. The company has a simple discount agreement that provides a discount to the list price of sofosbuvir-velpatasvir. The level of the discount is commercial in confidence.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Gilead and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of sofosbuvir-velpatasvir, having considered evidence on the nature of chronic hepatitis C and the value placed on the benefits

of sofosbuvir-velpatasvir by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need and practice

4.1 The committee heard from the clinical and patient experts that having treatment options that are free from peginterferon alpha, with or without ribavirin, is important to people with chronic hepatitis C because of the associated adverse reactions, which can lead to irreversible complications. The patient experts explained that some people refuse treatment with peginterferon alpha, which increases their risk of future complications associated with chronic hepatitis C infection. The committee noted that treatment with peginterferon alpha is gradually diminishing in clinical practice because of the introduction of newer direct-acting antivirals, particularly for genotypes 1 and 4 hepatitis C virus (HCV). However, it was aware that peginterferon alpha, with or without ribavirin, is still a major component of the treatment regimen for other HCV genotypes and agreed that there is an unmet need for interferon- and ribavirin-free regimens, particularly for genotype 3 HCV (which accounts for approximately 44% of the population of people with hepatitis C). The clinical experts considered that sofosbuvir-velpatasvir is a breakthrough treatment because of its simple dosing regimen, minimal adverse effects and interactions with other drugs, and effectiveness in decompensated cirrhosis (which may reduce the need for liver transplant). Therefore the committee recognised the importance of having an additional effective and tolerable treatment for people with chronic hepatitis C and concluded that sofosbuvir-velpatasvir could be a valuable option, especially for genotype 3 HCV.

Comparators for sofosbuvir-velpatasvir

4.2 The committee noted that the company did not include boceprevir and telaprevir (both taken in combination with peginterferon alpha and

ribavirin) as comparators because they are no longer used in clinical practice, although the NICE scope included them. The committee was also aware that the company had modelled some comparators in scenario analyses only (excluding them from its base case) because it considered they are not used in clinical practice. For example, daclatasvir with peginterferon alpha plus ribavirin, and simeprevir with peginterferon alpha plus ribavirin, in people with genotype 4 HCV. The committee heard from the clinical experts that boceprevir and telaprevir are not currently used in clinical practice in the UK, because the toxicities associated with peginterferon alpha plus ribavirin are worsened by adding other toxic treatments such as boceprevir or telaprevir. It heard that peginterferon alpha in combination with ribavirin and daclatasvir or simeprevir are not used to treat genotype 4 HCV because there are several interferon-free regimens available for this population. The committee concluded that it was appropriate to exclude these comparators from the analyses.

4.3 The committee was aware that the use of peginterferon alpha plus ribavirin is diminishing for some HCV genotypes (see section 4.1), and questioned the clinical experts about its relevance. It heard that peginterferon alpha plus ribavirin is the first choice treatment for people with mild, untreated genotype 2 HCV, and understood that its use for other HCV genotypes has not completely stopped. The committee concluded that peginterferon alpha plus ribavirin is a relevant comparator across all HCV genotypes.

4.4 The committee was aware that for people with decompensated cirrhosis, the company compared sofosbuvir-velpatasvir plus ribavirin with ledipasvir-sofosbuvir plus ribavirin. The committee understood that ledipasvir-sofosbuvir plus ribavirin has a marketing authorisation in the UK for decompensated cirrhosis, but that it is not recommended by NICE for this subgroup. It heard from the clinical experts that the clinical commissioning policy for chronic hepatitis C permits the use of ledipasvir-

sofosbuvir plus ribavirin in this population, and concluded that it is a relevant comparator.

Clinical effectiveness

Sustained virological response

4.5 The committee considered the key clinical evidence for sofosbuvir-velpatasvir, which came from 4 randomised controlled phase III clinical trials (ASTRAL-1, -2, -3 and -4). The trials included people who had not had treatment for their hepatitis C, and people whose hepatitis C had not adequately responded to interferon-based treatment. ASTRAL-1, -2 and -3 included people with compensated cirrhosis; ASTRAL-4 included people with decompensated cirrhosis. The committee was aware that the evidence review group (ERG) considered that the trials were generally well conducted, although there was a higher risk of bias in ASTRAL-2 and -3 because they were open-label studies. The committee noted that the results of the clinical trials showed high sustained virological response at 12 weeks irrespective of HCV genotype, cirrhosis stage or treatment history; the sustained virological response for sofosbuvir-velpatasvir ranged from 89% (for people with previously treated genotype 3 HCV and compensated cirrhosis) to 100% (in several subgroups). The committee concluded that the trials showed that sofosbuvir-velpatasvir is effective for treating chronic hepatitis C across all subgroups in all genotypes.

Adverse effects

4.6 The committee was aware that the most commonly reported adverse events are headache, fatigue and nausea. The committee noted that the results showed that sofosbuvir-velpatasvir has a relatively favourable tolerability profile, especially when compared with the peginterferon alpha plus ribavirin regimen. The committee concluded that the adverse events associated with sofosbuvir-velpatasvir are generally tolerable.

Cost effectiveness

Model structure

4.7 The committee noted that the structure of the model and its assumptions about the natural history of the disease are similar to models submitted for other NICE technology appraisals for chronic hepatitis C. It was aware that the company had grouped people with mild and moderate fibrosis into a single health state (non-cirrhotic), and agreed that this was consistent with how people are diagnosed in current practice. The committee concluded that the structure of the model is acceptable for decision-making.

Reinfection and future transmission of hepatitis C virus

4.8 The committee was aware that the company's base case model did not allow for reinfection after a sustained virological response, and that the ERG included an annual reinfection probability of 2.4% from a meta-analysis by Aspinall et al. 2013, which was presented in the company's response to clarification questions from NICE. The committee heard from the ERG that the model was sensitive to assumptions about reinfection. The clinical experts stated that 2.4% is an overestimate of the risk of reinfection, because most people having treatment for chronic hepatitis C are not current drug users and therefore their risk of reinfection is low. The clinical experts considered that the estimate of 2.4% was based on outdated studies that are not generalisable to the UK population. The committee noted that the company did not include a risk of future transmission of the virus in the model. It was aware that excluding reinfection may overestimate the health benefits of more effective treatments, and that excluding transmission may underestimate the benefits, but agreed that these opposing effects might not be equal. The committee agreed that it would have preferred to see a model including both reinfection and transmission, but appreciated that this would have needed a different (and potentially more complex) model structure. The

committee, noting the comments from clinical experts, agreed that the ERG's reinfection estimate of 2.4% was too high. It concluded that, in the absence of a model that incorporated both reinfection and transmission, cost-effectiveness results excluding reinfection and transmission (as in the company's base case) were acceptable for its decision-making.

Estimates of sustained virological response in the model

4.9 The committee noted that the sustained virological response rates for the comparators in the company's model were selected from individual arms of selected randomised controlled trials; the company used 1 source for each treatment in each subgroup. The committee was aware that the company could not perform network meta-analyses for all subgroups in the model, and agreed with the company's rationale for not including the results of its network meta-analysis to inform efficacy inputs in the model. The committee heard from the ERG that the company's choice of study for each comparator was often arbitrary; although the ERG considered that the company's justifications for each choice was valid, it suggested that equally valid justifications could have been provided for alternative sources. The committee was aware that the company's approach of selecting results from a single arm of a study means that the results were open to the risks of bias associated with observational studies. It noted that the company could have calculated a mean sustained virological response for each treatment in each subgroup using all available sources. The committee heard from the company that for 85 of the 118 sustained virological response rates used in the model, only 1 source was available. However the committee agreed with the ERG that, because each result was selected from a single arm of a study, the company should have included other study types such as uncontrolled and non-randomised studies. The committee concluded that the company's method of estimating efficacy in the model introduced some uncertainty in the results.

4.10 The committee noted that, according to the company's deterministic sensitivity analyses, the cost-effectiveness results were sensitive to the sustained virological response for peginterferon alpha plus ribavirin in people without cirrhosis; estimates for other comparators had less of an effect. The committee questioned the clinical experts on the appropriateness of the company's estimates of sustained virological response for peginterferon alpha plus ribavirin in people without cirrhosis, using the estimate of 71% in untreated genotype 3 HCV as an example. It heard from the company that 71% was a conservative estimate in this population, because the results of its meta-analyses (conducted in response to clarification questions from NICE) ranged from 59% to 67%. The committee questioned whether people with certain baseline characteristics such as mild disease, younger age and low viral load would have higher sustained virological response rates with peginterferon alpha plus ribavirin. It heard from the clinical experts that it is possible to identify people who are more likely to respond to peginterferon alpha plus ribavirin, but that this is not routine practice in the UK. The clinical experts suggested that the sustained virological response for peginterferon alpha plus ribavirin might be much lower than 71% for some populations, and agreed that the company's estimates were generalisable to current practice when considering the full population. Having concluded that the company's estimates of sustained virological response introduced some uncertainty in the results, but hearing that the rates for peginterferon alpha plus ribavirin were appropriate, the committee concluded that results based on the company's estimates of sustained virological response were acceptable for its decision-making.

Genotype-specific transition probabilities for developing compensated cirrhosis

4.11 The committee was aware that the company had assumed that progression from the non-cirrhotic to the compensated cirrhosis health state is faster in genotype 3 HCV than in other genotypes. The clinical

experts agreed with this assumption. The committee understood that this approach is consistent with previous NICE technology appraisals in hepatitis C, but noted that this is the first appraisal in which evidence supporting the calculation of HCV genotype-specific transition probabilities has been submitted. The committee heard from the clinical experts that the study selected by the company to inform these transition probabilities (Kanwal et al. 2014) is generalisable to current practice in the UK. However, the committee was concerned that the company had used unadjusted results from Kanwal et al. rather than the prespecified analyses which adjusted for patients' baseline characteristics. The company could not provide a rationale for using the unadjusted data, and the committee concluded that its decision-making should be based on analyses using the adjusted results from Kanwal et al., which the ERG had included in exploratory analyses for some subgroups.

Transition probabilities for disease progression in people with cirrhosis

4.12 The committee noted that the company had used transition probabilities for compensated or decompensated cirrhosis to hepatocellular carcinoma from Cardoso et al. 2010, and had not considered estimates from Fattovich et al. 1997 for these transitions. The committee heard from the company that this is consistent with previous NICE technology appraisals in chronic hepatitis C, and that the Cardoso data are more recent and therefore more appropriate. The committee recalled its conclusion from previous technology appraisals for hepatitis C that these transition probabilities lay somewhere between the estimates from Cardoso and Fattovich. It heard from the clinical experts that data from Fattovich et al. is generalisable to current practice, and was aware that the ERG had conducted exploratory analyses using transition probabilities from Fattovich et al. in some subgroups. The committee concluded that both sources should be taken into account in its decision-making.

Utility values

4.13 The committee was aware that the company used utility data from the literature in line with previous NICE technology appraisals for chronic hepatitis C (health state baseline values from Wright et al. 2006 and a utility increment after sustained virological response of 0.04 from Vera-Llonch et al. 2013). The committee noted the ERG's concerns that trial data are preferable to published utility values. It heard from the company that SF-36 data from the clinical trials of sofosbuvir-velpatasvir had not been formally mapped to produce SF-6D utility values for use in the economic model at the time of the submission. The committee emphasised that where available, it prefers utility values collected from the clinical trials of the intervention under evaluation to those estimated from other sources, but it was prepared to accept the estimates from Wright et al. and Vera-Llonch et al. in the economic analyses.

4.14 The committee was aware that the company had applied on-treatment utility increments (increased quality of life) and decrements (decreased quality of life), to represent the varying impact of different treatments. The committee understood that the company applied decrements for regimens containing peginterferon alpha or ribavirin to reflect the poor tolerability of these treatments. It understood that the company applied utility increments for direct-acting antivirals to reflect the benefits of rapidly suppressing the hepatitis C virus and the improved tolerability profile. The committee was concerned that the inclusion of treatment-specific changes in utility could lead to double counting, because the company also included utility increments for achieving sustained virological response and utility decrements for each adverse event, but it noted that the impact of removing them was negligible. The committee concluded that it was acceptable to include treatment-specific utility increments and decrements, but noted that there were uncertainties in the company's approach.

Pricing arrangements

4.15 The committee noted that the company has a simple discount agreement for sofosbuvir-velpatasvir (this discount is confidential). It also noted that confidential reduced contract prices for the comparators, agreed between each manufacturer and the Commercial Medicines Unit, were included in the analyses undertaken by the ERG, where known and if important to the committee's decision-making. The committee understood that the contract prices were the prices that the NHS pays for these treatments. The committee noted that NICE's guide to the methods of technology appraisal prefers using nationally available price reductions in the reference-case analysis to reflect the price relevant to the NHS. The committee concluded that the contract prices were the most relevant prices to the NHS and therefore the appropriate prices on which to base its decision.

Most plausible incremental cost-effectiveness ratios

4.16 The committee was aware that incremental cost-effectiveness ratios (ICERs) incorporating its preferred assumptions about transition probabilities (see sections 4.11 and 4.12) were available for only 2 subgroups: people with untreated genotype 2 HCV without cirrhosis, and people with untreated genotype 3 HCV without cirrhosis. The committee understood that, because of the large volume of subgroup analyses in the appraisal, the ERG could not do all of its exploratory analyses in all subgroups. The committee was aware that the ERG chose to focus on the comparison with peginterferon alpha plus ribavirin in untreated genotypes 2 and 3 HCV in people without cirrhosis because these were the comparisons which produced the highest ICERs for sofosbuvir-velpatasvir, in both the company's base case and the ERG's alternative base case. The committee noted that, in these 2 subgroups, using the adjusted data from Kanwal et al. increased the company's base case ICERs for sofosbuvir-velpatasvir by approximately £700–£2,700 per quality-adjusted life year (QALY) gained compared with peginterferon

alpha plus ribavirin. Using transition probabilities from Fattovich et al. instead of Cardoso et al. increased the ICERs for sofosbuvir-velpatasvir by approximately £2,500–£4,500 (table 2). Recalling its conclusion that the transition probabilities for disease progression lay somewhere between the Cardoso and Fattovich estimates, the committee concluded that the most plausible ICERs for sofosbuvir-velpatasvir compared with peginterferon alpha plus ribavirin lay between:

- £35,091 and £39,783 per QALY gained for people with untreated genotype 2 HCV and without cirrhosis
- £15,923 and £18,362 per QALY gained for people with untreated genotype 3 HCV and without cirrhosis.

Table 2 Incremental cost-effectiveness ratios for sofosbuvir-velpatasvir compared with peginterferon alpha plus ribavirin

		Source of transition probabilities for disease progression[a]	
		Cardoso 2010	**Fattovich 1997**
Untreated genotype 2 HCV without cirrhosis and eligible for interferon	Company base case (unadjusted data from Kanwal et al.)	£32,595	£37,125
	ERG exploratory analysis of company base case (adjusted data from Kanwal et al.)	£35,091	£39,783
Untreated genotype 3 HCV without cirrhosis and eligible for interferon	Company base case (unadjusted data from Kanwal et al.)	£15,199	£17,540
	ERG exploratory analysis of company base case (adjusted data from Kanwal et al.)	£15,923	£18,362

Abbreviation: HCV, hepatitis C virus
[a] except for the transition probabilities from the non-cirrhotic to compensated cirrhosis health state (taken from Kanwal et al. 2014)

4.17 The committee discussed the most plausible ICERs for sofosbuvir-velpatasvir compared with relevant comparators in all other subgroups, in which the company's base case ICERs were considerably lower than the ICERs for sofosbuvir-velpatasvir compared with peginterferon alpha plus ribavirin in genotypes 2 and 3 HCV. The

committee considered the likely impact of including its preferred assumptions on the company's base case ICER. It agreed that the ICERs would likely increase by a similar magnitude as in the 2 subgroups explored by the ERG and concluded that they would remain below £20,000 per QALY gained regardless of HCV genotype, treatment history and cirrhosis stage. Exact ICERs for all comparisons cannot be reported because the contract prices for the comparators in this appraisal are confidential and cannot be disclosed.

Recommendations

Genotypes 1 and 3–6 HCV

4.18 The committee agreed that at a willingness-to-pay threshold of £20,000 per QALY gained, and accounting for its preferred assumptions about transition probabilities, sofosbuvir-velpatasvir was cost effective compared with all comparators for HCV genotypes 1 and 3–6 regardless of genotype, treatment history and cirrhosis stage. The committee concluded that sofosbuvir-velpatasvir could be recommended for treating HCV genotype 1, 3, 4, 5 and 6 in people with:

- untreated disease and compensated cirrhosis
- untreated disease and without cirrhosis
- treated disease and compensated cirrhosis
- treated disease and without cirrhosis.

4.19 The committee noted that the marketing authorisation for sofosbuvir-velpatasvir states that ribavirin may be added to sofosbuvir-velpatasvir for people with genotype 3 HCV with compensated cirrhosis (see section 2). However it was not presented with analyses of sofosbuvir-velpatasvir in combination with ribavirin for this population. It noted that ribavirin has a much lower acquisition cost than sofosbuvir-velpatasvir, and agreed that adding ribavirin to the treatment regimen would likely have minimal impact on the ICERs, which were lower

in people with compensated cirrhosis than for people without cirrhosis. The committee agreed that, in practice, adding ribavirin to sofosbuvir-velpatasvir would be a clinical decision based on discussion between the patient and their clinician. The committee concluded that sofosbuvir-velpatasvir plus ribavirin could be recommended as a cost-effective use of NHS resources for treating people with genotype 3 HCV with compensated cirrhosis.

Genotype 2 HCV

4.20 The committee discussed the subgroup of people with genotype 2 HCV. It agreed that at a willingness-to-pay threshold of £20,000 per QALY gained, and accounting for its preferred assumptions about transition probabilities, sofosbuvir-velpatasvir was cost effective compared with all comparators for treated and untreated disease with compensated cirrhosis and for treated disease without cirrhosis. The committee concluded that sofosbuvir-velpatasvir could be recommended for treating genotype 2 HCV in people with:

- untreated disease and compensated cirrhosis
- treated disease and compensated cirrhosis
- treated disease and no cirrhosis.

4.21 The committee discussed the subgroup of people with untreated genotype 2 HCV who do not have cirrhosis. For people who can have interferon treatment, the committee noted that peginterferon alpha plus ribavirin is the only active treatment option because sofosbuvir plus ribavirin is only recommended for people with untreated disease if they cannot tolerate interferon or it is not suitable for them. The committee noted that the ICER for sofosbuvir-velpatasvir compared with peginterferon alpha plus ribavirin was above £20,000 per QALY gained when accounting for its preferred assumptions about transition probabilities. Therefore it concluded that sofosbuvir-velpatasvir could not be recommended as a cost-effective use of NHS resources for untreated

genotype 2 HCV in people without cirrhosis who can have interferon. For people who cannot tolerate interferon or it is not suitable for them, the committee noted that at a willingness-to-pay threshold of £20,000 per QALY gained, and accounting for its preferred assumptions about transition probabilities, sofosbuvir-velpatasvir was cost effective compared with sofosbuvir plus ribavirin. Therefore, the committee concluded that sofosbuvir-velpatasvir could be recommended as a cost-effective use of NHS resources for untreated genotype 2 HCV for people without cirrhosis, only if they cannot tolerate interferon or it is not suitable for them.

Decompensated cirrhosis

4.22 At a willingness-to-pay threshold of £20,000 per QALY gained, and accounting for its preferred assumptions about transition probabilities, sofosbuvir-velpatasvir plus ribavirin was cost effective compared with ledipasvir-sofosbuvir plus ribavirin. The committee concluded that sofosbuvir-velpatasvir plus ribavirin could be recommended as a cost-effective use of NHS resources for treating people with decompensated cirrhosis.

Other considerations

4.23 The committee was aware of NHS England's ongoing concerns about the increase in investment and capacity needed to make new oral treatments for hepatitis C available. The committee heard that the capacity to treat all eligible people with hepatitis C in the NHS according to NICE's recommendations is still constrained. It recalled that treatment decisions are influenced by clinical characteristics including HCV genotype, level of liver damage, comorbidities, and treatment history. With these factors in mind, people with chronic hepatitis C may accept treatment being prioritised for those with the highest unmet clinical need (including some people without cirrhosis), as determined by multidisciplinary teams.

Innovation

4.24 The committee agreed with the company that there is an unmet need for interferon- and ribavirin-free regimens in people with chronic hepatitis C, particularly for genotype 2 or 3 HCV, but concluded that these health gains are likely to have been included in the QALY calculations. The committee agreed that there were other benefits for people with chronic hepatitis C (for example, possible regression of fibrosis) and wider benefits to society (for example, reduced transmission of HCV, improved earning capacity) that were not captured in the QALY calculation and that, if taken into account, were likely to decrease the ICERs. However, the committee noted that it had taken these potential benefits into account when considering the cost effectiveness of sofosbuvir-velpatasvir and concluded that its recommendations for each population remained unchanged.

Equality issues

4.25 The committee noted the potential equality issues raised by the company and a professional organisation that there are proportionately more people from Asian and minority ethnic groups, and more people who inject drugs, in the genotype 3 HCV and genotype 4 HCV populations than in other HCV genotypes. Having decided that sofosbuvir-velpatasvir should be recommended for HCV genotypes 3 and 4, the committee agreed that its recommendations for these subgroups do not have a different impact on people protected by the equality legislation than on the wider population. The committee noted that its recommendations on the use of sofosbuvir-velpatasvir were irrespective of whether or not the person uses injectable drugs. The committee then discussed the subgroup in which it could not recommend sofosbuvir-velpatasvir as a cost-effective use of NHS resources: untreated genotype 2 HCV in people without cirrhosis, who can have interferon. The committee was aware, from the evidence discussed during a previous technology appraisal for hepatitis C, that the proportion

of people from Asian and minority ethnic groups was not disproportionately higher in genotype 2 HCV compared with other genotypes. It also noted that the ICER for sofosbuvir-velpatasvir compared with peginterferon alpha in untreated genotype 2 HCV without cirrhosis was substantially higher than £20,000 per QALY gained (ranging from £35,100 to £39,800). Based on the evidence presented, the committee agreed that its recommendations were fair and concluded that no further consideration of potential equality issues was needed to meet NICE's obligation to promote equality of access to treatment.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Sofosbuvir-velpatasvir for treating chronic hepatitis C**	**Section**
Key conclusion		
The committee concluded that the trials showed that sofosbuvir-velpatasvir is effective for treating chronic hepatitis C across all subgroups in all genotypes.		4.5
Sofosbuvir-velpatasvir is recommended as an option for treating chronic hepatitis C in adults, in the subgroups specified below, only if the company provides the drug with the discount agreed in the simple discount agreement.		1.1, 4.16–4.22
Genotypes 1 and 3–6 hepatitis C virus (HCV)		
The committee concluded that sofosbuvir-velpatasvir could be considered a cost-effective use of NHS resources for treating HCV genotype 1 and 3–6 regardless of genotype, treatment history and cirrhosis stage**.**		
The committee concluded that sofosbuvir-velpatasvir plus ribavirin could be considered a cost-effective use of NHS resources for		

treating people with genotype 3 HCV with compensated cirrhosis. **Genotype 2 HCV** The committee concluded that sofosbuvir-velpatasvir could be considered a cost-effective use of NHS resources for treating genotype 2 HCV in people with: • untreated disease and compensated cirrhosis • treated disease and compensated cirrhosis • treated disease and no cirrhosis. For people with untreated genotype 2 HCV who do not have cirrhosis, sofosbuvir-velpatasvir could be recommended as a cost-effective use of NHS resources only if interferon is not tolerated or not suitable. Sofosbuvir-velpatasvir was not recommended in people with untreated genotype 2 HCV who do not have cirrhosis and who can have interferon treatment, because of the high incremental cost-effectiveness ratio (ICER) compared with peginterferon alpha plus ribavirin. The ICER was between £35,100 (based on transition probabilities from Cardoso 2010) and £39,800 (based on transition probabilities from Fattovich 1997) per quality-adjusted life year (QALY) gained. **Decompensated cirrhosis** The committee concluded that sofosbuvir-velpatasvir plus ribavirin could be considered a cost-effective use of NHS resources for treating decompensated cirrhosis.		
Current practice		
Clinical need of patients, including	Some of the newer treatments for chronic hepatitis C are given in combination with	4.1

the availability of alternative treatments	peginterferon alpha or ribavirin. Having treatment options that are free from peginterferon alpha with or without ribavirin is important to people with chronic hepatitis C, particularly for people with genotype 3 HCV, because of the associated adverse reactions.	
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?	Sofosbuvir-velpatasvir has a simple dosing regimen and minimal adverse effects and interactions with other drugs. It is also effective in decompensated cirrhosis, which may reduce the need for liver transplant.	4.1
What is the position of the treatment in the pathway of care for the condition?	Sofosbuvir-velpatasvir provides another alternative to the existing oral treatment combinations for people with chronic hepatitis C, regardless of HCV genotype, treatment history and cirrhosis stage.	4.1
Adverse reactions	The adverse events associated with sofosbuvir-velpatasvir are generally tolerable.	4.6
Evidence for clinical effectiveness		
Availability, nature and quality of	The key clinical evidence for sofosbuvir-velpatasvir came from 4 randomised controlled phase III clinical trials	4.5

evidence	(ASTRAL-1, -2, -3 and -4). The evidence review group (ERG) considered that the trials were generally well conducted, although there was a higher risk of bias in ASTRAL-2 and -3 because they were open-label studies. The company could not perform network meta-analyses for all subgroups.	 4.9
Uncertainties generated by the evidence	The company's estimates of sustained virological response for all comparators were open to the risks of bias associated with observational studies, because the company selected them from individual arms of selected randomised controlled trials. The company should have included other study types and, although the company's justification for choosing each study was valid, equally valid justifications could have been provided for alternative sources.	4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Sofosbuvir-velpatasvir is effective for treating chronic hepatitis C across all subgroups in all genotypes.	4.5
Estimate of the size of the clinical effectiveness including strength of	Having noted the high sustained virological response rates as well as the ERG's comments that the trials were generally well conducted, the committee concluded that the trials showed that sofosbuvir-velpatasvir was	4.5

supporting evidence	effective for treating chronic hepatitis C.	
Evidence for cost effectiveness		
Availability and nature of evidence	The structure of the model was similar to models submitted for other NICE technology appraisals for chronic hepatitis C. The committee considered that grouping people with mild and moderate fibrosis into a single health state (non-cirrhotic) was consistent with how people are diagnosed in current practice. Although the marketing authorisation for sofosbuvir-velpatasvir states that ribavirin may be added to sofosbuvir-velpatasvir for people with genotype 3 HCV with compensated cirrhosis, the company did not present analyses of sofosbuvir-velpatasvir in combination with ribavirin for this population. The company excluded several comparators from its base case cost-effectiveness analyses: boceprevir, telaprevir and (for genotype 4 HCV) peginterferon alpha in combination with ribavirin and daclatasvir or simeprevir. The committee concluded that it was appropriate to exclude these comparators because they are not currently used in clinical practice in the UK.	4.7 4.19 4.2
Uncertainties around and plausibility of assumptions and	The committee agreed that not capturing the effect of reinfection and future transmission introduces uncertainty in the cost-	4.8

inputs in the economic model	effectiveness estimates, but concluded that the structure of the company's model was acceptable for decision-making. The company's method of estimating sustained virological response rates in the model introduced some uncertainty in the results. The company's inclusion of treatment-specific changes in utility might have led to double counting, but the impact of removing them was negligible. The company used unadjusted results from Kanwal et al. to estimate genotype-specific transition probabilities for developing compensated cirrhosis. Cost-effectiveness analyses using the prespecified adjusted results from Kanwal (performed by the ERG) were only presented for 2 subgroups. The company used transition probabilities for compensated or decompensated cirrhosis to hepatocellular carcinoma from Cardoso et al. 2010, and did not consider estimates from Fattovich et al. 1997. The committee agreed that these transition probabilities lay somewhere between the estimates from Cardoso and Fattovich. Cost-effectiveness analyses using the transition probabilities from Fattovich (performed by the ERG) were only	4.9, 4.10 4.14 4.11, 4.16 4.12, 4.16

	presented for 2 subgroups.	
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 emphasised that where available, it prefers utility values collected from the clinical trials of the intervention under evaluation to those estimated from other sources, but it was prepared to accept the estimates from Wright et al. and Vera-Llonch et al. in the economic analyses. The committee recognised the additional value of sofosbuvir-velpatasvir as an interferon- and ribavirin-free treatment but concluded that these health gains are likely to have been included in the QALY calculations. The committee agreed that there were other wider benefits to society (for example, reduced transmission of HCV), but noted that it had taken these potential benefits into account when considering the cost effectiveness of sofosbuvir-velpatasvir.	4.13 4.24
Are there specific groups of people for whom the technology is particularly cost effective?	At a willingness-to-pay threshold of £20,000 per QALY gained, sofosbuvir-velpatasvir was cost effective for all subgroups in all genotypes except for people with untreated genotype 2 HCV who do not have cirrhosis and who can have interferon treatment.	4.18–4.22
What are the key drivers of cost effectiveness?	The cost-effectiveness results were sensitive to the sustained virological response for peginterferon alpha plus ribavirin in people without cirrhosis (estimates for other	4.8, 4.10

	comparators had less of an effect). They were also sensitive to the rate of reinfection. Based on analyses in only 2 subgroups, the committee noted that the ICERs increased when the ERG used transition probabilities from Fattovich et al. 1997 and adjusted data from Kanwal et al. 2014.	 4.16
Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that the most plausible ICERs included adjusted data from Kanwal; did not include reinfection or transmission risk; and lay between the estimates based on transition probabilities from Cardoso and those that used transition probabilities from Fattovich. The committee was aware that ICERs incorporating these preferred assumptions were available for only 2 subgroups (presented by the ERG). The committee agreed that including its preferred assumptions in the analyses of the other subgroups would likely increase the ICERs by a similar magnitude as in the 2 subgroups explored by the ERG. At a willingness-to-pay threshold of £20,000 per QALY gained, and accounting for the committee's preferred assumptions, sofosbuvir-velpatasvir (in combination with ribavirin for treating decompensated cirrhosis) was cost effective for all subgroups in all genotypes except for people with untreated genotype 2 HCV who do not have cirrhosis	4.16, 4.17

	and who can have interferon treatment (for whom the ICER lay between £35,100 and £39,800 per QALY gained). Exact ICERs for all comparisons cannot be reported because the contract prices for the comparators in this appraisal are confidential and cannot be disclosed.	
Additional factors taken into account		
Pricing arrangements	The company has a simple discount agreement that provides a discount to the list price of sofosbuvir-velpatasvir. The level of the discount is commercial in confidence. Confidential reduced contract prices for the comparators were included in the analyses undertaken by the ERG, where known and if important to the committee's decision-making. The contract prices used in this appraisal are confidential and cannot be disclosed.	2, 4.15
End-of-life considerations	Not applicable	-
Equalities considerations and social value judgements	The company and professional groups raised the potential equalities issue that there are proportionately more people from Asian and minority ethnic groups in the genotype 3 and genotype 4 HCV populations than in other HCV genotypes. Having decided that sofosbuvir-velpatasvir should be recommended for HCV genotypes 3 and 4,	4.25

	the committee agreed that its recommendations for these subgroups do not have a different impact on people protected by the equality legislation than on the wider population. The committee also considered the population for whom it could not recommend sofosbuvir-velpatasvir (a subgroup of genotype 2 HCV). It was aware that the proportion of people from Asian and minority ethnic groups was not disproportionately higher in this genotype compared with other genotypes. Based on the evidence presented, the committee agreed that is recommendations were fair and concluded that no further consideration of potential equality issues was needed to meet NICE's obligation to promote equality of access to treatment.	

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.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must

usually provide funding and resources for it within 3 months of the guidance being published.

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

5.4 The company has arranged a simple discount agreement which provides a simple discount to the list price of sofosbuvir-velpatasvir. The level of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the discount should be directed to [NICE to add details at publication].

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
September 2016

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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.

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.

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.

Sophie Cooper
Technical Lead

Nwamaka Umeweni
Technical Adviser

Kate Moore
Project Manager

ISBN: [to be added at publication]