NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C

1 Recommendations

1.1 Sofosbuvir–velpatasvir–voxilaprevir is recommended as an option for treating chronic hepatitis C in adults, only if it is used as specified in table 1 and the company provides the drug at the same price or lower than that agreed with the Commercial Medicines Unit.

Table 1 Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C

Treatment history	Hepatitis C virus genotype	Liver disease stage	Recommendation
Previous direct-acting antivirals	1–6	With or without compensated cirrhosis	Recommended for 12 weeks
No direct-acting antivirals	3		Recommended for 8 weeks

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 These recommendations are not intended to affect treatment with sofosbuvir–velpatasvir–voxilaprevir that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding

arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Treatment options for chronic hepatitis C depend on the genotype of the virus and the person's cirrhosis status and treatment history. They include direct-acting antivirals (DAA) and interferon-containing treatments. There are currently no treatments with a marketing authorisation available for people who have had unsuccessful treatment with DAA.

Clinical trials show that sofosbuvir–velpatasvir–voxilaprevir is effective for treating all genotypes of chronic hepatitis C, irrespective of the person's cirrhosis status and treatment history.

The company's economic evidence is limited to people who have had DAA (genotypes 1–6) and people with genotype 3 hepatitis C who have not had DAA before. This reflects the groups with the highest unmet clinical need. Cost-effectiveness estimates for sofosbuvir–velpatasvir–voxilaprevir are within what NICE usually considers acceptable. Therefore sofosbuvir–velpatasvir–voxilaprevir can be recommended for these groups for treating chronic hepatitis C, as specified in table 1.

2 Information about sofosbuvir–velpatasvir–voxilaprevir

Marketing authorisation	Sofosbuvir–velpatasvir–voxilaprevir (Vosevi, Gilead Sciences) has a marketing authorisation in the UK for 'the treatment of chronic hepatitis C virus infection in adults'. This includes genotypes 1–6, with or without compensated cirrhosis, and includes people who have had previous treatment with direct-acting antivirals.
Dosage in the marketing authorisation	The recommended dose is 1 tablet taken orally once daily. Each tablet contains 400 mg sofosbuvir, 100 mg velpatasvir and 100 mg voxilaprevir. Treatment duration is 8 or 12 weeks depending on cirrhosis status and whether the person has had previous treatment with direct-acting antivirals. Please see the summary of product characteristics for more details.
Price	Sofosbuvir–velpatasvir–voxilaprevir costs £14,942.33 per 28-day pack. The total costs are £29,884.66 for an 8-week course and £44,826.99 for a 12-week course (company submission). The company agreed a nationally available price reduction for sofosbuvir–velpatasvir–voxilaprevir with the Commercial Medicines Unit. The contract prices agreed through the framework are commercial in confidence.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Gilead Sciences and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

A suitable treatment option is needed when direct-acting antivirals are unsuccessful

3.1 The use of interferon-containing treatments has reduced substantially in clinical practice because of the introduction of newer direct-acting antivirals (DAA) for hepatitis C. Clinical and patient experts stated that sofosbuvir–velpatasvir–voxilaprevir is effective when DAA have been

unsuccessful. This is particularly important because there are no NICE-recommended treatments available in this situation. The committee agreed with the clinical and patient experts that there is an unmet need when treatment with DAA is unsuccessful and sofosbuvir–velpatasvir–voxilaprevir is effective for genotypes 1–6 of hepatitis C in people who have had DAA before. Also, sofosbuvir–velpatasvir–voxilaprevir offers a short treatment duration for people who haven't had DAA before. The committee recognised that patients and clinicians would welcome an effective and tolerable treatment, especially for people who have had unsuccessful treatment with DAA before. It concluded that sofosbuvir–velpatasvir–voxilaprevir is a valuable treatment option.

Clinical effectiveness

Sofosbuvir–velpatasvir–voxilaprevir is effective for treating chronic hepatitis C

3.2 The key clinical evidence for sofosbuvir–velpatasvir–voxilaprevir came from 4 randomised controlled phase 3 clinical trials (POLARIS-1, -2, -3 and -4).

- Two trials recruited people who had previous DAA treatment (genotypes 1–6, with or without compensated cirrhosis) and compared 12-week sofosbuvir–velpatasvir–voxilaprevir treatment with placebo (POLARIS-1) or sofosbuvir–velpatasvir (POLARIS-4).
- Two trials recruited people who had no previous DAA treatment and compared 8-week sofosbuvir–velpatasvir–voxilaprevir treatment with sofosbuvir–velpatasvir in people with genotypes 1–6, with or without compensated cirrhosis (POLARIS-2) or in people with genotype 3 and compensated cirrhosis (POLARIS-3).

The ERG considered that the trials were generally well conducted, although there was a higher risk of bias in POLARIS-2, -3 and -4 because they were open-label studies, and because only POLARIS-1 randomised all patients. The trial results showed high sustained virological response at 12 weeks, ranging from 80% to 100%, irrespective of hepatitis C virus

genotype, cirrhosis stage or treatment history. The committee concluded that sofosbuvir–velpatasvir–voxilaprevir is effective for treating chronic hepatitis C across all subgroups and for genotypes 1–6.

Sofosbuvir–velpatasvir–voxilaprevir is generally well tolerated

3.3 The most commonly reported adverse events with sofosbuvir–velpatasvir–voxilaprevir were headache and fatigue. The patient expert noted that sofosbuvir–velpatasvir–voxilaprevir is a 3-agent treatment and therefore may result in more adverse events than a 2-agent treatment, but it is still generally tolerable. The committee agreed that sofosbuvir–velpatasvir–voxilaprevir has a relatively favourable safety and tolerability profile (irrespective of cirrhosis stage or treatment history) and concluded that the adverse events associated with sofosbuvir–velpatasvir–voxilaprevir were generally tolerable.

Cost-effectiveness analysis

The company's model structure is acceptable for decision-making

3.4 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. The ERG noted that treatment-related mortality and background mortality are related to treatment duration and can lead to counterintuitive results when comparing treatments of unequal durations. This is because the mortality in the model starts earlier for the shorter treatment. The company explained that this is a conservative assumption for sofosbuvir–velpatasvir–voxilaprevir because of the short treatment duration of 8 to 12 weeks. The committee 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 was acceptable for decision-making.

The population in the company's model is different to the population in the marketing authorisation

3.5 Although the marketing authorisation for sofosbuvir–velpatasvir–voxilaprevir includes treatment for people with hepatitis C genotypes 1–6 regardless of cirrhosis status and treatment history, the company included only 3 subgroups in its model:

- people who have had DAA (DAA-experienced; genotypes 1–6 with or without cirrhosis)
- people who have not had DAA (DAA-naive; genotype 3) without cirrhosis and
- people who have not had DAA (DAA-naive; genotype 3) with compensated cirrhosis.

The company explained that it focused on populations with high unmet clinical need. It emphasised that there are currently no other licensed treatments for disease previously treated with DAA, and that people with genotype 3 who have not had DAA are at highest risk of cirrhosis progression. The clinical experts and the representatives from NHS England agreed that there is an unmet need for people who have had DAA. They noted that other effective DAA treatments are available for people who have not had DAA (including for genotype 3). They confirmed that sofosbuvir–velpatasvir–voxilaprevir would mostly be used in clinical practice when previous DAA treatment has been unsuccessful. The committee was satisfied that the company's model reflected how the treatment would likely be used in clinical practice in England. Also, the comparators included by the company were those used in clinical practice for the included populations. Therefore it concluded that the company's approach was acceptable, and that subsequent discussions and recommendations would cover only the populations presented.

Reinfection and future transmission of hepatitis C is modelled as a scenario analysis for people with genotype 3 who have not had DAA

3.6 The company did a separate scenario analysis using dynamic transition modelling, which investigated the impact of onward transmission and reinfection for people with genotype 3 who have not had DAA. In the analysis, the company assumed that only people who inject drugs transmit hepatitis C or become reinfected after being cured. The results were similar to the results of the company's base case. The ERG explained that the scenario analysis made simplifying assumptions and was done only for people with genotype 3 who have not had DAA, with no results by cirrhosis status provided. In previous NICE chronic hepatitis C appraisals, the committee stated that it would have preferred to see a model including both reinfection and transmission. Having seen that the company's results were similar when both types of model structures were used, the committee concluded that the company's base-case model (excluding reinfection and transmission) was acceptable for decision-making.

The company's naive indirect comparison of sustained virological response rates leads to uncertainty in the model results

3.7 The company used a naive indirect comparison to compare sofosbuvir–velpatasvir–voxilaprevir with the relevant comparators in people with genotype 3 who have not had DAA. Because of the lack of comparative trial data for some of the comparators, an indirect treatment comparison was not feasible. The rates of sustained virological response for the comparators in the company's model were selected from individual arms of randomised controlled trials. The company used some of the same rates of sustained virological response for comparator technologies as those used in NICE's technology appraisal guidance on sofosbuvir–velpatasvir. The committee noted that this approach meant that the results were at risk of the kind of bias normally associated with observational studies. The ERG noted that the company combined the rates for people who had, and people who did not have, a previous treatment for the

sofosbuvir plus ribavirin treatment. But for the sofosbuvir plus peginterferon alfa and ribavirin treatment, it used only the rates for people who did not have a treatment before. The ERG combined the rates for people who had, and people who did not have, a previous treatment for sofosbuvir plus peginterferon alfa and ribavirin in its exploratory analyses; this had only marginal impact on the company's results. The committee agreed that for consistency, it preferred the ERG's approach to estimating the rates for sofosbuvir plus peginterferon alfa and ribavirin. It concluded that overall, the company's method of estimating efficacy in the model introduced some uncertainty in the results.

The company's transition probabilities with the ERG's amendment are appropriate for decision-making

3.8 The company used the same sources for non-treatment-specific transition probabilities as those used in NICE's technology appraisal guidance on sofosbuvir–velpatasvir. This included Kanwal et al. (2014) for genotype-specific fibrosis progression and Cardoso et al. (2010) for non-fibrosis progression (not genotype-specific). In its revision to the company's base case, the ERG applied a transition probability from a more recent source (Hepatitis C Trust, 2017) for progression from liver transplant to death. Also, the ERG explored using transition probabilities for compensated cirrhosis (to decompensated cirrhosis and hepatocellular carcinoma), decompensated cirrhosis (to hepatocellular carcinoma and death), and hepatocellular carcinoma (to death) from Fattovich et al. (1997) instead of Cardoso et al. in a scenario analysis, as recommended in the sofosbuvir–velpatasvir guidance. The ERG's analyses had only marginal impact on the company's results. The committee was generally satisfied with the company's approach, but preferred the ERG's approach of using more recent data sources to estimate transition probabilities for progression from liver transplant to death.

The committee prefers utility values from clinical trials, but it accepted the company's utility values

3.9 In its base-case analyses, the company used utility data from the literature (Wright et al. 2006 and Vera-Llonch et al. 2013) in line with NICE's previous technology appraisal guidance on hepatitis C. This was to inform the difference in utility of a health state with or without sustained virological response. The ERG stated that although EQ-5D was not an outcome in the POLARIS trials, health-related quality-of-life data were collected (for example, SF-36 data) and a review of utilities (especially for severe heath states) is needed. The committee noted that in the sofosbuvir–velpatasvir guidance it emphasised that, when available, utility values from the clinical trials are preferred. The committee accepted the company's base-case utility estimates, but stressed that in future hepatitis C appraisals, utility values from the literature will no longer be considered acceptable if there are utility values collected in clinical trials.

Treatment for 8 weeks is appropriate for people with genotype 3 and compensated cirrhosis who have not had direct-acting antivirals

3.10 For disease not previously treated with DAA, the marketing authorisation for sofosbuvir–velpatasvir–voxilaprevir recommends 12 weeks of treatment for people with compensated cirrhosis and suggests 8 weeks for people with genotype 3. The company modelled 8-week treatment in its base case, in line with the clinical trials for genotype 3 hepatitis C in this population, but presented a scenario analysis using 12-week treatment. The analyses suggested that extending treatment to 12 weeks in this population increased the incremental cost-effectiveness ratio (ICER) significantly. The clinical experts acknowledged that people with compensated cirrhosis normally have treatment for 12 weeks using the new DAA treatments. However, they stated that 8-week treatment with sofosbuvir–velpatasvir–voxilaprevir is effective for genotype 3 and could possibly be implemented in clinical practice in line with the clinical trials. They further noted that DAA treatments are already available for this population. The committee agreed that 8-week treatment is appropriate

for people with genotype 3 and compensated cirrhosis. It will consider both the 8-week and 12-week treatments for people with genotype 3 and compensated cirrhosis who have not had DAA in its decision-making.

Cost-effectiveness results

Sofosbuvir–velpatasvir–voxilaprevir is cost effective

3.11 The committee's preferred assumptions were based on the ERG's revisions to the company's base case, including:

- the more consistent estimation of sustained virological response for sofosbuvir plus peginterferon alfa and ribavirin in people with genotype 3 who have not had DAA (95.1% and 87.9% for non-cirrhotic and cirrhotic disease respectively; see section 3.7)
- the more recent transition probability from liver transplant to death (16% and 5.2% in year 1 and subsequent years respectively; see section 3.8)
- increasing the proportion of mild compared with moderate fibrosis in the non-cirrhotic state (from a 83:17 split to a 50:50 split) to better reflect clinical experience and
- decreasing the length of follow-up for people without cirrhosis who had a sustained virological response from 2 years to 1 year to better reflect clinical practice.

Using the committee's preferred assumptions and the confidential price discounts for sofosbuvir–velpatasvir–voxilaprevir and its comparators, the ICERs for sofosbuvir–velpatasvir–voxilaprevir were below £20,000 per quality-adjusted life year (QALY) gained, except for the scenario with 12-week treatment for sofosbuvir–velpatasvir–voxilaprevir for people with genotype 3 and compensated cirrhosis who have not had DAA. In this scenario, the ICER was considerably above the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained). So 12-week treatment for sofosbuvir–velpatasvir–voxilaprevir in this subgroup could not be

recommended. The committee concluded that sofosbuvir–velpatasvir–voxilaprevir was cost effective for the populations in the company's base-case analysis. It can be recommended for treating chronic hepatitis C:

- as a 12-week treatment for people with genotypes 1–6 (with or without compensated cirrhosis) who have had DAA and
- as an 8-week treatment for people with genotype 3 (with or without compensated cirrhosis) who have not had DAA before.

Other factors

Treatment and prescribing decisions

3.12 Previous NICE technology appraisal guidance on hepatitis C included recommendations on treatment and prescribing decisions because of capacity constraints within the NHS. The clinical experts stated that many people eligible for treatment, particularly people with cirrhosis, have now had treatment creating additional capacity to treat more. The clinical experts also stated that having more affordable drugs with shorter treatment durations also creates additional capacity. However, NHS England commented that there is considerable value in the existing NICE recommendation for multidisciplinary teams in the operational delivery networks to prioritise treatment for people with the highest unmet clinical need and the need for its continuation. NHS England considers that removing this wording would create major challenges and that the capacity constraints within the NHS have not changed sufficiently for the recommendation to be removed at this present time. On balance, after considering arguments both for and against, the committee accepted it was appropriate to continue to include the recommendation on this aspect (see section 1.2) as in previous NICE guidance for the oral hepatitis C treatments.

Innovation

3.13 The committee considered whether sofosbuvir–velpatasvir–voxilaprevir could be considered innovative, and whether the company's economic

analysis had captured all associated health-related benefits. The committee agreed with the company that there is an unmet need for people who have had unsuccessful treatment with DAA. However, the committee concluded that it had taken these potential benefits into account when considering the cost effectiveness of sofosbuvir–velpatasvir–voxilaprevir.

Equality

3.14 The committee noted potential equality issues raised during the NICE scoping process. Chronic hepatitis C disproportionately affects some populations such as certain immigrant populations, prison populations, and drug users, in terms of accessing the healthcare system and having access to innovative new treatments. In addition, the Haemophilia Society suggested that this treatment should be a priority for people with a bleeding disorder. Having decided that sofosbuvir–velpatasvir–voxilaprevir should be recommended for all the groups for whom there was evidence presented, the committee agreed that its recommendations were fair. It concluded that no further consideration of potential equality issues was needed to meet NICE's obligation to promote equality of access to treatment.

4 Implementation

4.1 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.

4.2 The Welsh ministers have 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 2 months of the first publication of the final appraisal determination.

4.3 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 hepatitis C and the doctor responsible for their care thinks that sofosbuvir–velpatasvir–voxilaprevir is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The contract price used for decision-making in this appraisal is the relevant price that the NHS pays for sofosbuvir–velpatasvir–voxilaprevir. This is based on contract pricing arrangements between Gilead and the Commercial Medicines Unit. Contract prices are commercial in confidence. Any enquiries from NHS organisations about the contract prices used in this appraisal should be directed to the Commercial Medicines Unit.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Lindsay Smith
Chair, appraisal committee
January 2018

6 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.

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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.

Marcela Haasova
Technical Lead

Nwamaka Umeweni
Technical Adviser

Kate Moore
Project Manager

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