Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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sofosbuvir 400mg, velpatasvir 100mg film-coated tablets (Epclusa®)
SMC No. (1195/16)

Gilead Sciences Ltd

07 October 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sofosbuvir-velpatasvir (Epclusa®) is accepted for restricted use within NHS Scotland.

Indication under review: Treatment of chronic hepatitis C virus (HCV) infection in adults.

SMC restriction: in patients with genotype 3 (GT3) chronic HCV infection.

Sofosbuvir-velpatasvir for 12 weeks, compared with sofosbuvir plus ribavirin for 24 weeks, significantly improved sustained virologic suppression in adults with genotype 3 chronic HCV infection.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 07 November 2016

Indication

Treatment of chronic hepatitis C virus (HCV) infection in adults.

Dosing Information

One tablet, swallowed whole, once daily with or without food. Due to the bitter taste, the film-coated tablet should not be chewed or crushed.

In patients without cirrhosis or with compensated cirrhosis treatment should be continued for 12 weeks and the addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis.

In patients with decompensated cirrhosis treatment should be combined with ribavirin and continued for 12 weeks.

In patients who have previously failed therapy with an NS5A-containing regimen treatment should be combined with ribavirin and continued for 24 weeks.

Treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.

Product availability date

15 July 2016

Summary of evidence on comparative efficacy

Sofosbuvir-velpatasvir fixed-dose combination (Epclusa®) is the second fixed-dose formulation of the nonstructural protein 5B (NS5B) RNA polymerase inhibitor, sofosbuvir, in combination with a nonstructural protein 5A (NS5A) inhibitor licensed for treatment of chronic hepatitis C virus (HCV) infection.[1] The company has requested that SMC considers sofosbuvir-velpatasvir when positioned for use in patients with genotype 3 (GT3) chronic HCV.

An open-label phase III study (ASTRAL-3) recruited 552 treatment-experienced and treatment-naive adults with chronic (≥six months) GT3 HCV. Patients were stratified by cirrhosis (presence or absence) and previous treatment (naive or experienced) then randomised equally to orally administered sofosbuvir 400mg plus velpatasvir 100mg fixed-dose combination once daily for 12 weeks or to sofosbuvir 400mg once daily plus ribavirin twice daily (daily dose 1,000mg if <75kg and 1,200mg if ≥75kg) for 24 weeks. The primary outcome was sustained virologic response, defined as HCV RNA below the limit of quantification, 15 units/mL, at 12 weeks after the end of treatment (SVR12). This was assessed using Cochran-Mantel-Haenszel test in all randomised patients who received at least one dose of study drug for non-inferiority and then for superiority.[2]

Sofosbuvir plus velpatasvir, compared with sofosbuvir plus ribavirin, significantly increased SVR12, 95% (264/277) versus 80% (221/275), with a difference of 15% (95% confidence interval [CI]: 9.6 to 20), p<0.001. SVR12 rates were 97% (191/197) versus 87% (163/187) in

patients without cirrhosis and 91% (73/80) versus 66% (55/83) in patients with cirrhosis, with treatment differences of 9.8% (95% CI: 4.2% to 15.7%) and 25% (95% CI: 11.5% to 37.2%) in the respective subgroups. Similarly, the respective regimens were associated with SVR12 of 97% (200/206) versus 86% (176/204) in treatment-naive patients and 90% (64/71) versus 63% (45/71) in treatment-experienced patients, with treatment differences of 10.8% (95% CI: 5.3% to 16.5%) and 26.8% (95% CI: 12.2% to 40.1%) in the respective subgroups. Sofosbuvir plus velpatasvir was associated with high SVR12 across most subgroups as indicated in table 1.[1,2]

Table 1: SVR12 in ASTRAL-3[1]

	Treatment-naive		Treatment-experienced	
	No cirrhosis	**Cirrhosis**	**No cirrhosis**	**Cirrhosis**
Sofosbuvir plus velpatasvir 12 weeks	98% (160/163)	93% (40/43)	91% (31/34)	89% (33/37)
Sofosbuvir plus ribavirin 24 weeks	90% (141/156)	73% (33/45)	71% (22/31)	58% (22/38)

SVR12 = sustained virologic response 12 weeks after the end of treatment.

The European Medicines Agency (EMA) noted that the Y93H mutation in GT3 was the only naturally occurring NS5A resistance-associated variant that had a relevant impact on treatment outcome with sofosbuvir plus velpatasvir. Y93H occurs in slightly less than 10% of untreated patients with GT3 at baseline and is universally found in patients with GT3 who have failed therapy with sofosbuvir plus a NS5A inhibitor (including velpatasvir). In the 25 patients who had Y93H at baseline, SVR12 with sofosbuvir plus velpatasvir was 84% (21/25). However, it was 50% (2/4) in those with cirrhosis and 90.5% (19/21) in those without cirrhosis. SVR12 was 96% (242/251) in patients without Y93H at baseline. In the sofosbuvir plus velpatasvir group, 43 patients had NS5A resistance-associated variants (A30K, L31M and Y93H) at baseline and SVR12 was achieved by 88% (38/43) compared with 97% (225/231) of patients without these mutations. Ten patients had NS5B resistance-associated variants at baseline and all achieved SVR12.[2]

Of the 13 patients in the sofosbuvir plus velpatasvir group who did not achieve SVR12, eleven had virologic failure after the end of treatment and two were lost to follow-up.[8] Virologic failures with sofosbuvir plus velpatasvir were infrequent in patients without cirrhosis, 2.0%, but increased to 8.8% in those with compensated cirrhosis and similar patterns were observed for baseline NS5A resistance-associated variants (2.6% versus 11.6%), treatment-experience (1.9% versus 9.9%), and high viral load of HCV ≥800,000 units/mL (1.2% versus 5.2%).[10]

In the open-label phase III study (ASTRAL-4) in adults with chronic HCV and decompensated cirrhosis, defined as Child-Pugh-Turcotte class B sofosbuvir 400mg plus velpatasvir 100mg fixed-dose combination once daily for 12 weeks or for 24 weeks or this fixed-dose combination plus ribavirin twice daily for 12 weeks produced SVR12 rates of 50% (7/14), 50% (6/12) and 85% (11/13), respectively, within the subgroup of patients who had GT3.[4] Virological failure (relapse or on-treatment failure) was noted for 43% (6/14), 42% (5/12) and 15% (2/13) of patients in the respective groups. One patient in the 12 week sofosbuvir plus velpatasvir plus ribavirin group had on-treatment failure and pharmacokinetic data indicated non-compliance.[1]

In an ongoing open-label phase III study (ASTRAL-5) in adults with chronic HCV and human immunodeficiency virus, sofosbuvir 400mg plus velpatasvir 100mg fixed-dose combination once daily for 12 weeks produced SVR12 rate of 92% (11/12) in the subgroup of the patients with GT3. The patient who did not achieve SVR12 withdrew consent during the study.[5]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The EMA noted that the favourable safety profile of the NS5B inhibitor, sofosbuvir, was well established and that of velpatasvir was in line with other NS5A inhibitors. The safety profile of sofosbuvir plus velpatasvir was considered to be unremarkable.[10] In the ASTRAL-3 study within the sofosbuvir plus velpatasvir group, compared with the sofosbuvir plus ribavirin group, rates of adverse events were 88% (245/277) versus 95% (260/275). Serious adverse events were reported in the respective groups by 2.2% (6/277) versus 5.5% (15/275) of patients.

Common adverse events were generally reported at similar or lower rates with sofosbuvir plus velpatasvir compared with sofosbuvir plus ribavirin. These included fatigue (26% versus 38%), headache (32% in both groups), nausea (17% versus 21%), insomnia (11% versus 27%), irritability (8.3% versus 15%), pruritus (2.9% versus 13%), cough (5.0% versus 13%), nasopharyngitis (12% in both groups) and dyspepsia (3.2% versus 11%). In the sofosbuvir plus ribavirin group there were increased rates of adverse events commonly associated with ribavirin including fatigue, insomnia, irritability, pruritus, cough and dyspepsia.[2]

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

The submitting company has requested that SMC considers sofosbuvir plus velpatasvir when positioned for use in patients with GT3 chronic HCV. Sofosbuvir plus velpatasvir (Epclusa®) is the second fixed-dose formulation of the NS5B inhibitor, sofosbuvir, plus a NS5A inhibitor for HCV. The first, sofosbuvir plus ledipasvir (Harvoni®), is licensed for use over 24 weeks in combination with ribavirin for patients with GT3 who have compensated cirrhosis and/or prior treatment failure. It has been accepted by SMC for restricted use in those ineligible for interferon. The NS5A inhibitor, daclatasvir, is licensed for 12 weeks' use in combination with sofosbuvir for patients with GT3 without cirrhosis. This was the first ribavirin- and interferon-free regimen for HCV, comprising a NS5A inhibitor and a NS5B inhibitor. Sofosbuvir plus velpatasvir is the second. Daclatasvir is also licensed for 24 weeks use in combination with sofosbuvir ± ribavirin for patients with GT3 and cirrhosis.[1,6,7]

In the pivotal ASTRAL-3 study, the primary outcome of SVR12, which is recommended by the EMA as an appropriate primary outcome for studies assessing cure rate,[8,9] was significantly improved by 15% with 12 weeks sofosbuvir plus velpatasvir compared with 24 weeks sofosbuvir plus ribavirin. Sofosbuvir plus velpatasvir produced high SVR12 rates across most subgroups defined by previous treatment and cirrhosis.[2] However, the EMA noted that the majority of patients with cirrhosis had mild cirrhosis and in those with more severe, yet still compensated, cirrhosis there was a trend towards increased risk of relapse. This corresponds with high

relapse (and low SVR12) rates with sofosbuvir plus velpatasvir in GT3 subgroup of the ASTRAL-4 study in patients with more severe (i.e. decompensated) cirrhosis. In the latter study, the addition of ribavirin to sofosbuvir plus velpatasvir decreased treatment failure. Treatment options for patients with GT3 and cirrhosis who fail sofosbuvir plus velpatasvir are unclear and this is a problematic issue. Therefore, the summary of product characteristics (SPC) recommends that addition of ribavirin to 12 weeks sofosbuvir plus velpatasvir be considered for GT3 patients with cirrhosis and should be undertaken for those with decompensated cirrhosis. The Y93H resistance-associated variant was also noted to have an impact on the outcome of sofosbuvir plus velpatasvir treatment in patients with GT3, especially those with cirrhosis. This mutation is universally found in patients with GT3 who fail treatment with sofosbuvir plus NS5A inhibitor. The SPC recommends that sofosbuvir plus velpatasvir be combined with ribavirin and continued for 24 weeks in patients who have previously failed therapy with an NS5A-containing regimen.[1,10]

The open-label design of the ASTRAL-3 study may have limited assessment of subjective outcomes, such as adverse events and quality-of-life. The study was not designed to provide data on one-year relapse rates or long-term clinical outcomes, and no other evidence was provided. There were limited numbers of patients aged over 65 years. However, it is noted that SVR12 observed for patients ≥65 years was similar to that of patients <65 years. There were also limited numbers of patients with genotypes other than GT3a.[1,2]

Treatment of HCV infection has been evolving with the introduction of new medicines and new indications since the introduction of the first direct-acting antiviral (DAA) in 2011. Also, as indicated in national guidelines,[11] treatment choice depends upon previous treatment, presence of cirrhosis and eligibility for interferon. This creates challenges in the identification of relevant comparators and estimation of relative treatment effects. The situation is compounded by limited clinical data for some regimens and evolving treatment regimens.

There were no direct comparisons for sofosbuvir plus velpatasvir versus regimens recommended in the national guidelines for treatment of GT3 chronic HCV infection. The submission estimated relative treatment efficacy versus relevant comparators by applying data from selected studies to the economic analysis to form naïve indirect comparisons. In treatment-naive interferon-eligible adults, 12 weeks sofosbuvir plus velpatasvir was compared with 12 weeks sofosbuvir, peginterferon alpha plus ribavirin as the main comparator and with 24 weeks peginterferon alpha plus ribavirin, which is an option for those with low viral load and minimal fibrosis. In treatment-naïve interferon-ineligible adults, the comparator was 12 weeks sofosbuvir plus daclatasvir plus ribavirin. This regimen was also a comparator, along with 12 weeks sofosbuvir plus ledipasvir plus ribavirin, in treatment-experienced interferon-ineligible adults. The naïve indirect comparisons were limited by small sample size of subgroups from which data were derived, particularly for patients with cirrhosis, lack of baseline data within the subgroups to assess heterogeneity and failure to compare one-year relapse rates, other longer-term outcomes or quality-of-life. The indirect comparisons were also limited by the choice of studies to estimate treatment effect in practice for certain regimens, which may not be optimal due to issues with external validity.

Clinical experts consulted by SMC considered that sofosbuvir plus velpatasvir for GT3 chronic HCV infection was a therapeutic advancement due to its efficacy and safety profile. They advised that it may replace other therapies and be used for all patients with GT3 chronic HCV infection.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing sofosbuvir plus velpatasvir to a range of different comparator treatments in patients with genotype 3 chronic hepatitis C. The analysis was presented according to a patient's previous treatment experience, eligibility for interferon-based treatment and cirrhosis status. The comparators considered for each grouping is shown in the table below:

Table 2: Comparators by patient group

Patient group	Comparators considered
Treatment-naive	(1) Sofosbuvir plus peginterferon plus ribavirin for 12 weeks (2) Peginterferon plus ribavirin for 24 weeks (3) No treatment
Treatment-naive and ineligible for interferon	(1) Sofosbuvir plus daclatasvir for 12 weeks (2) No treatment
Treatment-experienced and ineligible for interferon	(1) Sofosbuvir plus daclatasvir plus ribavirin for 12 weeks (2) Ledipasvir plus sofosbuvir plus ribavirin for 12 week (3) No treatment

The company indicated that while a variety of populations were presented, the focus of the submission was treatment-naive patients. The submitting company considered that sofosbuvir plus peginterferon plus ribavirin was the main comparator in treatment-naive patients. SMC clinical experts did, however, note that some patients were being treated with peginterferon and ribavirin and thus this was also a relevant comparator.

A lifetime Markov state transition model was used for the various analyses and included health states for SVR, compensated and decompensated cirrhosis, hepatocellular carcinoma, and liver transplant. The model structure did not differentiate between mild and moderate disease among non-cirrhotic patients. Treatment-naive patients were assumed to be aged 40 years at the start of the model and treatment-experienced patients were assumed to be aged 45 years.

The key clinical variable driving the model was the SVR. For sofosbuvir plus velpatasvir, these data were taken from the pivotal ASTRAL-3 study. For the comparator treatments, data were taken from a naive indirect comparison or by assumption. For example, for the sofosbuvir plus daclatasvir plus ribavirin regimen, the SVR for 12 weeks sofosbuvir plus daclatasvir was used as a proxy. Achieving an SVR was essentially a cure for patients who start the model in the non-cirrhotic state as they reverted to normal population risks for the remainder of the model. Patients who achieved an SVR but started in the cirrhotic state are still exposed to a risk of moving to the decompensated cirrhotic state or the heptatocellular carcinoma state.

For later transitions through the health states in the model, transition probabilities were taken from published literature and largely consistent with values used in other health technology assessments. It should be noted that a higher transition rate than has been seen in previous models for genotype 3 patients was assumed for patients moving from the non-cirrhotic health state to the compensated cirrhosis state, which the company said was reflective of genotype 3 disease being associated with faster disease progression.

Utility values on treatment were estimated from literature sources for all states of the model. For example, a non-cirrhotic patient was assumed to have a baseline quality of life score of 0.75, and achieving an SVR increased quality of life by 0.04, which is common to other health technology assessments of hepatitis C treatments. Quality of life while on treatment was also taken into account and it is noted that a patient treated with sofosbuvir plus velpatasvir was assumed to have an on-treatment utility increment of 4.43% (based on data from using the ledipasvir plus sofosbuvir regimen) whereas all other treatment regimens were assumed to have a utility decrement applied (ranging from -14.77% for peginterferon plus ribavirin to -1% for sofosbuvir plus daclatasvir plus ribavirin).

Health state costs were largely taken from published sources and similar to health state costs used in other economic models.

Using incremental analysis, the relevant results for the various scenarios are shown below:

Table 3: Base case results

Comparison	**Incremental costs**	**Incremental quality adjusted life years (QALYs)**	**Incremental cost-effectiveness ratio (ICER)**
Interferon-eligible, treatment naive, non-cirrhotic patients			
Sofosbuvir plus velpatasvir versus peginterferon plus ribavirin (other comparators ruled out on dominance or extended dominance)	£29,872	1.24	£24,090
Interferon-eligible, treatment naive, cirrhotic			
Sofosbuvir plus velpatasvir versus sofosbuvir plus peginterferon plus ribavirin	£997	0.11	£9,064
Interferon-ineligible, treatment naive, non-cirrhotic			
Sofosbuvir plus velpatasvir versus no treatment (sofosbuvir plus daclatasvir plus ribavirin was dominated by sofosbuvir plus velpatasvir)	£23,504	4.41	£5,330
Interferon-ineligible, treatment naive, cirrhotic			
Sofosbuvir plus velpatasvir versus no treatment (sofosbuvir plus daclatasvir plus ribavirin dominated by sofosbuvir plus velpatasvir)	£24,934	4.84	£5,152
Interferon- ineligible, treatment-experienced, non-cirrhotic			
Sofosbuvir plus velpatasvir versus no treatment (sofosbuvir plus daclatasvir plus ribavirin and sofosbuvir plus ledipasvir both dominated by sofosbuvir plus velpatasvir)	£25,058	3.61	£6,941
Interferon-ineligible, treatment-experienced, cirrhotic			
Sofosbuvir plus velpatasvir versus no treatment (sofosbuvir plus ledipasvir dominated by sofosbuvir plus velpatasvir)	£24,431	4.33	£5,642

The company also presented results from the pairwise (rather than incremental) analysis for the interferon-eligible, treatment-naive, non-cirrhotic group versus what they considered to be the main comparator to be (sofosbuvir plus peginterferon plus ribavarin). This resulted in a cost per QALY of £6,118 on the basis of a QALY gain of 0.14 and incremental costs of £868.

Deterministic sensitivity analysis showed that the results were relatively stable for the treatment-experienced patients, remaining under £15,000 per QALY. However, for the treatment-naive patients, the sensitivity analysis showed that the ICERs were particularly sensitive to the costs of the treatment regimens and the SVRs assumed. Sensitivity analysis for the interferon-eligible, treatment naive, non-cirrhotic group versus peginterferon plus ribavarin remained under £30,000 per QALY except when the SVR efficacy difference was changed, resulting in an ICER of £33,461. Against sofosbuvir plus peginterferon plus ribavarin, the ICER rose to a maximum of £46,630 when the SVR for sofosbuvir plus velpatasvir fell from 99.6% to 95.6%. In treatment-naive cirrhotic patients sofosbuvir plus velpatasvir was dominated by sofosbuvir plus peginterferon plus ribavarin when the SVR for the comparator regimen increased from 91.3% to 98.88% or when the SVR for sofosbuvir plus velpatasvir fell from 93.2% to 83.4%.

A number of weaknesses or uncertainties were noted with the analysis:

- The analysis was driven by naive indirect comparisons and as such there is uncertainty associated with the relative efficacy of the new regimen compared to existing treatments and the sensitivity analysis showed that the results were sensitive to the SVR.
- The SVR rates assumed for the daclatasvir regimens may not be representative of rates achieved in practice, as the EMA has suggested that these would be greater than those with the sofosbuvir plus ribavirin regimen (i.e. greater than 82% to 92%). The cost-effectiveness ratios associated with this comparison may therefore be more uncertain. However, given the higher costs associated with the daclatasvir regimen, it is likely that even if SVRs equivalent to the rate for sofosbuvir plus velpatasvir were assumed, sofosbuvir plus velpatasvir would remain cost-effective.
- The base case analysis assumed an on-treatment utility gain for the regimen, compared to utility losses for the other treatments. However, removing on-treatment effects only caused small increases in the ICERs, given the relatively short durations of treatment in the context of a lifetime model. For example, in treatment naïve, interferon-eligible non-cirrhotic patients, the ICER versus peginterferon plus ribavirin increased to £25,315.
- As noted, the analysis assumed a higher rate of transition from the non-cirrhotic to the compensated cirrhotic state than has been seen in previous SMC submissions; the company has clarified that this was based on an updated literature search. The company was asked to provide some additional sensitivity analysis to show the impact of changing this assumption to the value seen in previous evaluations. This resulted in increases in the ICER, most notably for the treatment-naive non-cirrhotic patients where the ICER versus peginterferon plus ribavirin rose to £39,837, with other ICERs rising to between around £10k and £13k. While the use of an updated source of data is reasonable, it is noted that the choice of value exerts an influence on the results.
- The analysis assumed unlicensed 12 week treatment durations for some of the comparators. However, SMC clinical experts have indicated that the shorter treatment durations would be used in clinical practice. In addition, it should be noted that the economic model did not consider a 24 week sofosbuvir plus velpatasvir plus ribavirin regimen in patients who have previously failed therapy with an NS5A-containing regimen and thus the cost-effectiveness of this regimen has not been assessed.

Despite these weaknesses or uncertainties, the economic case was demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from the Hepatitis C Trust and Hepatitis Scotland.
- The Hepatitis C Trust has received 50% pharmaceutical company funding in the past two years, including from the submitting company. Hepatitis Scotland has received 0.85% pharmaceutical company funding in the past two years, but none from the submitting company.
- Hepatitis C is a blood-borne virus that predominantly infects liver cells. This can result in inflammation and significant damage to the liver. The resultant damage to the liver means that people living with the disease can be seriously debilitated. It is a significantly stigmatised disease that can affect employability. All these factors mean that diagnosis can have a devastating impact on the patient, their family and carers.
- Hepatitis C is curable but therapies vary in effectiveness and tolerability. Current treatment regimens are long, and interferon-containing treatment regimens in particular have significant side effects. Not all patients can tolerate them.
- Sofosbuvir plus velpatasvir offers an effective treatment for Hepatitis C. It is an oral regimen with a shorter treatment time and a tolerable side-effect profile. There is less need for frequent hospital visits and a reduced number of blood tests during treatment, which enables more patients to be treated without any significant disruption to their working and family lives.

Additional information: guidelines and protocols

In December 2015 Healthcare Improvement Scotland and NHS National Services Scotland published National Clinical Guidelines for the treatment of HCV in adults, version 2.0. For GT3 infected patients, with or without cirrhosis, sofosbuvir, peginterferon plus ribavirin for 12 weeks is recommended. For those with low viral load and mild to moderate fibrosis peginterferon plus ribavirin for 16 to 24 weeks is recommended as an option. The interferon-free regimens of 12 weeks sofosbuvir, daclatasvir plus ribavirin and 12 weeks ledipasvir, sofosbuvir plus ribavirin are recommended as options for patients with cirrhosis who are ineligible for interferon. The ledipasvir-containing regimen is also recommended first-line for treatment-experienced interferon-ineligible patients without cirrhosis, while the daclatasvir-containing regimen is recommended for second-line treatment of these patients if they have Metavir F3.[11]

In July 2013 the Scottish Intercollegiate Guidelines Network (SIGN) issued publication number 133: management of hepatitis C. These guidelines pre-date the availability of DAA for GT3.[12]

In February 2016 the British Society of Gastroenterology published consensus treatment recommendations for the management of patients with chronic HCV infection. These recommend 24 weeks peginterferon alpha plus ribavirin for treatment-naive patient with fibrosis Metavir ≤F3 and 12 weeks sofosbuvir, peginterferon alpha plus ribavirin for all other patients

(i.e. treatment-naive with cirrhosis and treatment experienced patients). Sofosbuvir, daclatasvir ± ribavirin for 12 weeks is recommended for interferon ineligible patients who are treatment-naive and treatment-experienced and have fibrosis with Metavir F3 or cirrhosis.[13]

Additional information: comparators

A variety of regimens are licensed for treatment of GT3 chronic HCV and these are detailed in the table below. National guidelines[11] provide recommendations on appropriate treatments for individual patients based on previous treatment, presence of cirrhosis and interferon eligibility. These are summarised above.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Sofosbuvir plus velpatasvir	**400mg/100mg orally once daily for 12 weeks**	**38,980**
Sofosbuvir plus velpatasvir Ribavirin	**400mg/100mg orally once daily for 12 weeks 1,000 to 1,200mg orally once daily for 12 weeks**	**39,783**
Sofosbuvir plus velpatasvir Ribavirin	**400mg/100mg orally once daily for 24 weeks 1,000 to 1,200mg orally once daily for 24 weeks**	**79,566**
Sofosbuvir Daclatasvir Ribavirin	400mg orally once daily for 24 weeks 60mg orally once daily for 24 weeks 1,000 to 1,200mg orally once daily for 24 weeks	120,609*
Sofosbuvir plus ledipasvir Ribavirin	400mg/90mg orally once daily for 24 weeks 1,000 to 1,200mg orally once daily for 24 weeks	79,567**
Sofosbuvir Daclatasvir	400mg orally once daily for 12 weeks 60mg orally once daily for 12 weeks	59,501
Sofosbuvir Peginterferon alpha 2a Ribavirin	400mg orally once daily for 12 weeks 180micrcogram SC once weekly for 12 weeks 1,000 to 1,200mg orally once daily for 12 weeks	37,279
Peginterferon alpha 2a Ribavirin	180microgram SC once weekly for 24 weeks 1,000 to 1,200mg orally once daily for 24 weeks	4,593

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 3 July 2016, except sofosbuvir plus velpatasvir, which are from the new product assessment form. Costs are based on a body weight of 70kg, equating to a ribavirin dose of 1,000mg daily. Costs of unlicensed 12 week courses would be * £60,304 and ** £39,784.SC = subcutaneous injection.

Additional information: budget impact

The submitting company estimated there would be 623 patients eligible for treatment with sofosbuvir plus velpatasvir in all years. The estimated uptake rate was 96% in year 1 (598 patients), reducing to 76% in year 5 (474 patients).

The gross impact on the medicines budget was estimated to be £23m in year 1 and £18m in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £8m in year 1 and £7m in year 5.

References

The undernoted references were supplied with the submission.

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12. Scottish Intercollegiate Guidelines Network. Publication number 133: management of hepatitis C, July 2013.
13. British Society of Gastroenterology. Treatment recommendations for the management of patients with Chronic HCV Infection, February 2016.

This assessment is based on data submitted by the applicant company up to and including 16 September 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.