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 1271/17

Gilead Sciences Ltd

08 September 2017

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 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 2, 5 or 6 chronic HCV infection
- decompensated cirrhosis, irrespective of chronic HCV genotype

Sofosbuvir-velpatasvir was associated with high rates of sustained virologic suppression in adults with genotype 1, 2, 4, 5 and 6 chronic HCV infection, including those with decompensated cirrhosis. Sofosbuvir-velpatasvir was associated with significantly superior sustained virologic suppression compared with sofosbuvir plus ribavirin in adults with genotype 2 chronic HCV infection.

SMC has issued separate advice accepting the use of sofosbuvir-velpatasvir for the treatment of patients with genotype 3 chronic HCV infection.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of sofosbuvir-velpatasvir. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Published 09 October 2017

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.[1]

In patients without cirrhosis or with compensated cirrhosis treatment should be continued for 12 weeks. In patients with decompensated cirrhosis treatment should be combined with ribavirin and continued for 12 weeks. In patients who have previously failed therapy with a non-structural protein 5A (NS5A)-containing regimen treatment should be combined with ribavirin and continued for 24 weeks.[1]

Treatment should be initiated and monitored by a physician experienced in the management of patients with HCV infection.[1]

Product availability date

6 July 2017

Summary of evidence on comparative efficacy

Sofosbuvir-velpatasvir (Epclusa®) is a fixed-dose formulation of the NS5B inhibitor, sofosbuvir, in combination with the NS5A inhibitor, velpatsavir. It is licensed for treatment of all genotypes (GT1 to 6) of chronic hepatitis C virus (HCV) infection.[1] Following a full submission, in which it was positioned for use in patients with GT3 infection, SMC issued advice (number 1195/16) in November 2016 that sofosbuvir-velpatasvir is accepted for restricted use within NHS Scotland in patients with GT3 chronic HCV infection. This submission relates to the other genotypes included in the licence, i.e. GT1, GT2, GT4, GT5 and GT6.

There were 624 and 266 adults, respectively, with chronic (≥six months) HCV infection treated in a double-blind study (ASTRAL-1) of GT1, 2, 4, 5 or 6 and an open-label study (ASTRAL-2) of GT2. In both studies patients were either treatment-experienced (defined as prior treatment failure to a regimen containing interferon either with or without ribavirin) or treatment-naive and up to 20% could have compensated cirrhosis. In ASTRAL-1 patients were stratified by GT (1, 2, 4, 6 or indeterminate) and by cirrhosis (presence or absence). The study aimed to recruit 20 patients with GT5 and they were not randomised, but all assigned to the sofosbuvir-velpatasvir group. The other patients were randomised in a 5:1 ratio to sofosbuvir 400mg, velpatasvir 100mg fixed-dose combination once daily for 12 weeks or placebo. In ASTRAL-2 patients were stratified by cirrhosis (presence or absence) and previous treatment (naive or experienced) then randomised equally to 12 weeks of sofosbuvir 400mg, velpatasvir 100mg fixed-dose combination once daily or sofosbuvir 400mg once daily plus ribavirin twice daily (daily dose 1,000mg in patients <75kg and 1,200mg in patients ≥75kg). All study drugs were administered orally. In both studies, the primary outcome was sustained virologic response, defined as HCV RNA below the lower limit of quantification, 15units/mL, 12 weeks after the end of treatment (SVR12). This was assessed in all patients who received at least one dose of study drug.[2-4]

In ASTRAL-1, SVR12 with sofosbuvir-velpatasvir was 99% (618/624), which was significantly greater than the pre-specified performance goal of 85%. There were no SVR12 responses with placebo. Subgroup analyses by genotype are detailed in table 1. In ASTRAL-2 SVR12 with sofosbuvir-velpatasvir was significantly greater than that with sofosbuvir plus ribavirin: 99% (133/134) versus 94% (124/132), with a strata-adjusted absolute difference of 5.2% (95% confidence interval [CI]: 0.2 to 10.3), p=0.02.[2-4]

An open-label phase III study (ASTRAL-4) recruited treatment-experienced and treatment-naive adults with chronic (≥six months) GT 1 to 6 HCV who had decompensated cirrhosis, defined as Child-Pugh-Turcotte (CPT) class B (i.e. a score of 7 to 9 on a scale ranging from 5 to 15 with higher scores indicating more advanced liver disease). After stratification for genotype they were randomised equally to sofosbuvir 400mg, velpatasvir 100mg fixed-dose combination once daily for 12 weeks or for 24 weeks or this fixed-dose combination once daily plus ribavirin twice daily (daily dose 1,000mg in patients <75kg and 1,200mg in patients ≥75kg) for 12 weeks. All study drugs were administered orally. The primary outcome SVR12 was assessed in all randomised patients who received at least one dose of study treatment. In the respective groups SVR12 rates were 83% (75/90), 86% (77/90) and 94% (82/87) and each was significantly superior compared with the pre-specified assumed spontaneous response rate of 1%. Subgroup analyses by genotype are detailed in table 1.[2,5]

In an open-label phase III study (ASTRAL-5) 106 treatment-experienced and treatment-naive adults with chronic (≥six months) GT 1 to 6 HCV and human immunodeficiency virus (HIV) infection received sofosbuvir 400mg, velpatasvir 100mg fixed-dose combination once daily for 12 weeks. The primary outcome, SVR12, was achieved by 95% (101/106) of patients. Subgroup analyses by genotype are detailed in table 1.[6]

Table 1: SVR12 subgroup analyses for GT1a, 1b, 2, 4, 5 and 6 in ASTRAL-1, -4 and -5.[2-6]

	SVR12 Response Rates					
	GT1a	**GT1b**	**GT2**	**GT4**	**GT5**	**GT6**
ASTRAL-1						
Sofosbuvir-Velpatasvir 12 weeks	98% (206/210)	99% (117/118)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)
ASTRAL-4 (decompensated cirrhosis)						
Sofosbuvir-Velpatasvir 12 weeks	88% (44/50)	89% (16/18)	100% (4/4)	100% (4/4)	-	-
Sofosbuvir-Velpatasvir 24 weeks	93% (51/55)	88% (14/16)	75% (3/4)	100% (2/2)	-	100% (1/1)
Sofosbuvir-Velpatasvir ribavirin 12 weeks	94% (51/54)	100% (14/14)	100% (4/4)	100% (2/2)	-	-
ASTRAL-5 (HIV co-infection)						
Sofosbuvir-Velpatasvir 12 weeks	95% (63/66)	92% (11/12)	100% (11/11)	100% (5/5)	-	-

SVR12 = sustained virologic response 12 weeks after end of treatment; GT = genotype; HIV = human immunodeficiency virus.

Summary of evidence on comparative safety

The European Medicines Agency (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-velpatasvir was considered to be unremarkable.[2]

In ASTRAL-2, within the sofosbuvir-velpatasvir and sofosbuvir plus ribavirin groups, adverse events were reported by 69% (92/134) and 77% (101/132) respectively, with low rates of serious adverse events (two patients in each group) and discontinuation due to adverse events (one patient in the sofosbuvir-velpatasvir group). Common adverse events were generally reported at similar or lower rates in the sofosbuvir-velpatasvir group versus sofosbuvir plus ribavirin group. These included fatigue (15% versus 36%), headache (18% versus 22%), nausea (10% versus 14%), insomnia (4.5% versus 14%), irritability (3.0% versus 6.8%), pruritus (4.5% versus 5.3%), cough (3.0% versus 4.5%), nasopharyngitis (6.0% versus 1.5%) and dyspepsia (0.8% versus 3.8%). 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.[4]

In ASTRAL-4 within the sofosbuvir-velpatasvir plus ribavirin, sofosbuvir-velpatasvir 12 week and 24 week groups adverse events were reported by 91% (79/87), 81% (73/90) and 81% (73/90), respectively, with serious adverse events reported by 16% (14/87), 19% (17/90) and 18% (16/90), respectively. Discontinuation due to adverse events was uncommon: four, one and four patients in the respective groups. Common adverse events were generally reported at similar or higher rates in the sofosbuvir-velpatasvir plus ribavirin group versus sofosbuvir-velpatasvir 12 week and 24 week groups. These included fatigue (39% versus 26% and 23%), nausea (25% versus 24% and 20%), headache (21% versus 26% and 19%), anaemia (31% versus 4.4% and 3.3%), diarrhoea (21% versus 6.7% and 7.8%), insomnia (14% versus 10% and 10%), pruritus (4.6% versus 11% and 4.4%), muscle spasm (11% versus 3.3% and 4.4%), dyspnoea (10% versus 4.4% and 2.2%) and cough (10% versus 2.2% and 0).[5]

Summary of clinical effectiveness issues

Sofosbuvir-velpatasvir fixed-dose combination (Epclusa®) is the second fixed-dose formulation of the NS5B inhibitor, sofosbuvir, in combination with a NS5A inhibitor licensed for treatment of chronic HCV infection.[1]

HCV is a blood borne viral infection that can lead to liver cirrhosis and hepatocellular carcinoma. The national clinical guideline for the treatment of HCV in adults provides guidance on the place in therapy of currently available medicines. The guideline is based on the principle developed by HCV Treatment and Therapies Sub-group of the National Sexual Health and Blood Borne Virus Advisory Committee, which states that patients should expect that the likelihood of cure with their initial treatment is at least 90% and this should be achieved with minimal side effects. The guideline advice is detailed below in the additional guidelines and protocols section.[7]

In patients with no or compensated cirrhosis, the licensed regimen of 12-week sofosbuvir-velpatasvir was associated with high SVR12 rates of at least 97% and these were superior to placebo, in patients with GT1a, 1b, 2, 4, 5 and 6 (in ASTRAL-1). In patients with CPT class B decompensated cirrhosis, the licensed regimen of 12-week sofosbuvir-velpatasvir plus ribavirin was associated with similarly high SVR12 rates of at least 94% in patients with GT1a, 1b, 2 and 4

(in ASTRAL-4). In the ASTRAL-2 study 12-week sofosbuvir-velpatasvir was superior to 12-week sofosbuvir plus ribavirin in patients with GT2 and no or compensated cirrhosis (including treatment-naive and treatment-experienced). There are no direct comparative data relative to the peg-interferon plus ribavirin regimen, which is recommended in the national guideline for treatment-naive patients with GT2.[2-5]

It was noted by the EMA that the cirrhotic patients included in ASTRAL-1 and -2 may be considered to have fairly mild cirrhosis with modest baseline Fibroscan values in the majority of these patients. Consequently, patients with more severe but compensated cirrhosis were under-represented in the study program. In this context, the high SVR12 rates observed in the ASTRAL-4 study in patients with decompensated CPT class B cirrhosis provide key additional evidence to support efficacy in patients with severe compensated cirrhosis.[2]

The ASTRAL studies were not designed to provide data on one-year relapse rates or long-term clinical outcomes. The open-label design of the ASTRAL-2 and -4 studies may have limited assessment of subjective outcomes, such as adverse events and quality of life. Patients with HBV infection were excluded from the sofosbuvir-velpatasvir studies and this limits application of both efficacy and safety data in these groups.[2]

There are no direct comparative data versus relevant comparators for many of the subgroups defined by genotype, previous treatment and cirrhosis. SVR12 data from the relevant group or subgroup within a study selected (sometimes from several available studies) as representative were applied directly to economic analyses, forming naive indirect comparisons, for all except the GT2 cohort. Across all GT1 cohorts, SVR12 rates were greater than 90% and the principle of assumed efficacy equivalence advised in the national guideline can generally be applied to sofosbuvir-velpatsavir and the comparators, specifically the recently marketed direct-acting anti-virals (DAA) listed in that guideline. The ASTRAL-2 study provided direct comparative data for 12-week sofosbuvir-velpatasvir versus the relevant comparator in treatment-experienced GT2 patients, 12-week sofosbuvir plus ribavirin. A Bucher indirect comparison of 12-week sofosbuvir-velpatasvir versus 24-week peg-interferon plus ribavirin was performed in the treatment-naive GT2 cohort and results were applied to the economic analysis. There were some limitations with the indirect comparison including, uncertainty around the choice of study as representative of the comparator treatment and small sample size, especially for cirrhotic subgroups. There was also a possible issue with external validity with respect to the treatment effect of 90% noted in the national guideline for the peg-interferon regimen. For the GT4, 5 and 6 cohorts, which are uncommon in Scotland, SVR12 rates were generally above 90% for regimens including a DAA. However, the indirect comparisons supported by these were limited by small sample size for much of the input data.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing sofosbuvir-velpatasvir to a range of different comparator treatments in patients with genotype 1, 2, 4, 5, and 6 chronic HCV. 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 2. SMC clinical experts have indicated that gazoprevir- elbasvir is viewed as a key comparator for genotype 1 and 4 patient groups.

Table 2: Comparator treatments used in the economic evaluation

Patient group	Comparators considered
Genotype 1	Grazoprevir-elbasvir (GZV/EBV) Ledipasvir-sofosbuvir (LDV/SOF) Ombitasvir-paritaprevir-ritonavir + dasabuvir +/- ribavirin (3D/RBV) Sofosbuvir + pegylated interferon + ribavirin (SOF/IFN/RBV) No treatment
Genotype 2	Sofosbuvir + ribavirin (SOF/RBV) Pegylated interferon + ribavirin No treatment
Genotypes 4, 5, 6	Grazoprevir-elbasvir Ledipasvir-sofosbuvir Ombitasvir-paritaprevir-ritonavir + ribavirin Sofosbuvir + pegylated interferon + ribavirin No treatment
Decompensated cirrhosis	Ledipasvir-sofosbuvir + ribavirin (SOF/LDV/RBV)

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 at the start of the model and treatment-experienced patients were assumed to be aged 45. Patients with decompensated cirrhosis were assumed to be aged 55 and 60 relative according to their prior treatment experience, respectively.

The key clinical variable driving the model was the SVR. For sofosbuvir- velpatasvir these data were taken from the pivotal ASTRAL-1 and ASTRAL-2 studies. For the comparator treatments, data were taken from a naive indirect comparison or Bucher indirect comparison (comparison with Peg-IFN/RBV in GT2 patients). Patients who achieve an SVR but started in the cirrhotic state are still exposed to a risk of moving to the decompensated cirrhotic state or the HCC 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 was assumed for patients moving from the non-cirrhotic health state to the compensated cirrhosis state than has been seen in previous models.

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 base line 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 pegylated interferon-free and ribavirin-free regimen was assumed to have an on-treatment utility increment of 4.43% (based on data from ledipasvir-sofosbuvir regimens) whereas all other treatment regimens were assumed to have a utility decrement applied (ranging from -14.77% for pegylated interferon + ribavirin to -1% for ombitasvir-paritaprevir-ritonavir + dasabuvir + ribavarin).

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

A patient access scheme was submitted by the company and assessed by the Patient Access Scheme Assessment Group [PASAG] as acceptable for implementation in NHS Scotland. Under the PAS a discount was offered on the list price of the medicine. A PAS is in place for grazoprevir-elbasvir and this was included in the results used for decision-making by SMC by using an estimate of the comparator PAS price.

The results presented do not take account of the PAS for grazoprevir-elbasvir or the PAS for sofobuvir-velpatasvir but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for grazoprevir-elbasvir due to commercial confidentiality and competition law issues Additionally, SMC would wish to present the cost-effectiveness estimates including the sofosbuvir-velpatasvir PAS but is unable to do so owing to commercial in confidence concerns. As such, the results are presented using the list price of both sofosbuvir-velpatasvir and grazoprevir-velpatasvir.

Using incremental analysis, the without PAS results for the various scenarios are shown in table 3 below:

Table 3: Cost-effectiveness results

Geno-type	Sub-group	Comparator	Incremental costs using list prices	Incremental quality adjusted life years (QALYs)	Incremental cost-effectiveness ratios (ICERs) using list prices
GT1a	TN NC	GZV/EBV	£2,007	0.13	£15,985
	TN CC	GZV/EBV	£2,055	0.14	£14,403
	TE NC	GZV/EBV	£2,182	0.08	£27,243
	TE CC	GZV/EBV	£1,662	0.23	£7,191
GT1b	TN NC	GZV/EBV	£1,629	0.21	£7,690
	TN CC	GZV/EBV	£2,785	-0.07	Dominated
	TE NC	GZV/EBV	£1,830	0.16	£11,779
	TE CC	GZV/EBV	£2,407	0.04	£62,495
GT1	TN NC	GZV/EBV	£1,873	0.16	£12,009
	TN CC	GZV/EBV	£2,313	0.07	£33,404
	TE NC	GZV/EBV	£2,057	0.11	£19,293
	TE CC	GZV/EBV	£1,925	0.16	£11,799
GT2 IE	TN NC	IFN/RBV	£31,591	0.60	£52,247
	TN CC	IFN/RBV	£28,821	1.42	£20,366
	TE NC	IFN/RBV	£22,377	1.72	£13,045
	TE CC	IFN/RBV	£18,361	2.89	£6,358
GT2 II	TN NC	SOF/RBV	£2,182	0.11	£20,331

	TN CC	SOF/RBV	£1,443	0.34	£4,214
	TE NC	SOF/RBV	£296	0.50	£595
	TE CC	SOF/RBV	£2,687	0.00	Dominated
GT4	TN NC	GZV/EBV	£1,173	0.34	£3,484
	TN CC	GZV/EBV	£2,658	0.00	Dominated
	TE NC	GZV/EBV	-£417	0.65	Dominant
	TE CC	GZV/EBV	-£1,317	1.03	Dominant
GT5	TN NC	No treatment	£26,680	3.28	£8,126
	TN CC	SOF/IFN/RBV	-£7,503	2.52	Dominant
	TE NC	No treatment	£26,537	2.97	£8,942
	TE CC	SOF/IFN/RBV	-£7,680	2.34	Dominant
GT6	TN NC	No treatment	£26,168	3.40	£7,698
	TN CC	SOF/IFN/RBV	-£7,503	2.52	Dominant
	TE NC	No treatment	£26,537	2.97	£8,942
	TE CC	SOF/IFN/RBV	-£7,680	2.34	Dominant
DCC	TN	SOF/LDV/RBV	-£7,346	0.16	Dominant
	TE	SOF/LDV/RBV	-£7,536	0.15	Dominant

GT: genotype, TN: treatment-naïve, TE: treatment-experienced, NC: non-cirrhotic, CC: compensated cirrhosis, DCC: decompensated cirrhosis, IE: interferon-eligible, II: interferon-ineligible
GZV/EBV: grazoprevir-elbasvir (12 weeks),
SOF/LDV/RBV: ledipasvir-sofosbuvir + ribavirin (12 weeks),
SOF/IFN/RBV: sofosbuvir + pegylated interferon + ribavirin (12 weeks)
SOF/RBV: sofosbuvir + ribavirin (12 weeks)
IFN/RBV: pegylated interferon + ribavirin (24 or 48 weeks)

Genotype 1 and 4 results (comparison with grazoprevir-elbasvir)
Sofosbuvir-velpatasvir often showed ICERs per QALY of approximately £7k to £62k in GT1 patients (without the PAS or comparator PAS). In GT4 patients, the ICERs varied from sofosbuvir-velpatasvir being dominated to being dominant.

Genotype 2
Sofosbuvir-velpatasvir without PAS was dominated (more expensive, less effective) in treatment-experienced cirrhotic interferon- ineligible patients and showed an ICERs per QALY of below £53k in the remaining subgroups.

Genotypes 5 and 6 and decompensated cirrhosis
The resulting ICERs per QALY for sofosbuvir-velpatasvir without PAS were lower than £9k, in some scenarios, and sofosbuvir-velpatasvir was even dominant (cheaper, more effective) over some treatment options.

There are a number of issues with the analyses presented:

- The analysis was driven mainly by naive indirect comparisons for GT1, 4, 5, and 6 and Bucher indirect comparison for GT2, and as such there is uncertainty associated with the relative efficacy of the new regimen compared to existing treatments. Moreover, the analysis for GT4, 5 and 6 was based on data from small subgroups of patients, which adds to uncertainty associated with the results. The gain in outcomes was rather small and uncertain in the major subgroups of GT1 and GT4 and showed some variability to different SVR rates in sensitivity analysis.
- There was some uncertainty surrounding the use of utility increments and decrements associated with the different safety profile of individual combinations which were also based on

indirect evidence. However, the company presented additional scenarios and showed that these utility adjustments have only a small impact on results.

- The analysis assumed usually only the shorter treatment durations for some of the comparators. However, SMC clinical experts have indicated that the shorter treatment durations would be also used in clinical practice.

Given these issues and the relevant cost-effectiveness results considered by SMC, the economic case was demonstrated only in patients with genotype 2, 5, and 6 HCV or in patients with decompensated cirrhosis.

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

Summary of patient and carer involvement

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

- We received a patient group submission from The Hepatitis C Trust, which is a registered charity.

- The Hepatitis C Trust has received 50% pharmaceutical company funding in the past two years, including 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 January 2017 Healthcare Improvement Scotland (HIS) and NHS National Services Scotland published National Clinical Guidelines for the treatment of HCV in adults, version 3.0. Treatment recommendations are presented according to genotype and summarised in the table below.[7]

Classification	Recommended regimen
Genotype 1	
Treatment-naïve non-cirrhotic	ombitasvir, paritaprevir, ritonavir, dasabuvir +/- ribavirin (12 weeks) sofosbuvir, ledipasvir (eight weeks) sofosbuvir, simeprevir (12 weeks) sofosbuvir, daclatasvir (12 weeks) (F3-F4 only) elbasvir, grazoprevir (12 weeks)*
Treatment-experienced non-cirrhotic	ombitasvir, paritaprevir, ritonavir, dasabuvir +/- ribavirin (12 weeks) sofosbuvir, ledipasvir (12 weeks) sofosbuvir, daclatasvir (12 weeks) (F3-F4 only) elbasvir, grazoprevir (12 weeks)*
Cirrhotic irrespective of previous treatment	ombitasvir, paritaprevir, ritonavir, dasabuvir +/- ribavirin (12 weeks) sofosbuvir, ledipasvir + ribavirin (12 weeks) sofosbuvir, daclatasvir + ribavirin (12 weeks) elbasvir, grazoprevir +ribavirin (12 weeks)*
Genotype 2	
Interferon-eligible	Peg interferon alpha +ribavirin (16-24 weeks)
Interferon ineligible or treatment-experienced	sofosbuvir + ribavirin (12 weeks)
Genotype 4, 5 and 6	
All patients	Genotypes 4, 5 and 6 are uncommon in Scotland. Treatments should be prescribed according to local protocols or where appropriate, expert advice sought.

Additional information: comparators

In practice the main comparator appears to be elbasvir-grazoprevir (Zepatier®) in GT1 infection, with other DAA regimens as alternative options. The main comparators in GT2 infection are peg-interferon alpha plus ribavirin for treatment-naïve interferon-eligible patients and sofosbuvir plus ribavirin for treatment-experienced patients or treatment-naïve interferon-ineligible patients. Several regimens containing DAA are treatment options for GT4, 5 and 6 infections.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
Sofosbuvir-velpatasvir	**One tablet daily for 12 weeks**	**38,980**
Sofosbuvir-velpatasvir Ribavirin	**One tablet daily for 16 weeks 1,000 to 1,200mg daily for 16 weeks**	**39,783 to 39,944**
Daclatasvir Sofosbuvir Ribavirin	60mg orally once daily for 12 weeks 400mg orally once daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	60,304 to 60,465
Daclatasvir Sofosbuvir	60mg orally once daily for 12 weeks 400mg orally once daily for 12 weeks	59,501
Sofosbuvir Simeprevir	400mg orally once daily for 12 weeks One tablet daily for 12 weeks	57,621
Elbasvir-grazoprevir Ribavirin	One tablet daily for 16 weeks 1,000 to 1,200mg daily for 16 weeks	49,738 to 49,952
Ledipasvir-sofosbuvir Ribavirin	One tablet daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	39,784 to 39,944
Ledipasvir-sofosbuvir	One tablet daily for 12 weeks	38,980
Elbasvir-grazoprevir	One tablet daily for 12 weeks	36,500
Ombitasvir-paritaprevir-ritonavir Dasabuvir Ribavirin	Two tablets once daily for 12 weeks One tablet twice daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	35,804 to 35,965
Sofosbuvir Ribavirin	400mg orally once daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	35,786 to 35,947
Ombitasvir-paritaprevir-ritonavir Dasabuvir	Two tablets once daily for 12 weeks One tablet twice daily for 12 weeks	35,000
Ledipasvir-sofosbuvir	One tablet daily for 8 weeks	25,987
Peg-interferon-alpha-2b Ribavirin	1.5mcg/kg once weekly for 16 to 24 weeks 800 to 1,200mg daily for 16 to 24 weeks	3,198 to 4,797*
Peg-interferon-alpha-2a Ribavirin	180mcg once weekly for 16 to 24 weeks 800 to 1,200mg daily for 16 to 24 weeks	2,848 to 4,914

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 June 2017. Dose regimens are from the national guideline and choice depends on disease classification, (see table in the Additional information: guidelines and protocols section above). Costs do not take any patient access schemes into consideration. costs for both peg-interferon-alpha-2b and ribavirin based on 70kg body weight.*

Additional information: budget impact

The submitting company estimated there would be 131 patients eligible for treatment with sofosbuvir-velpatasir in all years to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

1. Gilead Sciences. Summary of product characteristics for Epclusa®, last updated 14 June 2017.
2. European Medicines Agency. European public assessment report for Epclusa, Committee for Medicinal Products in Human Use (CHMP) assessment report EMA/399285/2016, 26 May 2016.
3. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5 and 6 infection. N Engl J Med 2015; 373: 2599-607.
4. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med 2015; 373(27): 2608-17.
5. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015; 373: 2618-28.
6. Wyles D, Brau N, Kottilil S, et al. Sofosbuvir and velpastasvir for the treatment of hepatitis C virus in patients coinfected with human immunodeficiency virus type-1: an open-label, phase 3 study. Clin Infect Dis 2017; 65: 6-12.
7. Healthcare Improvement Scotland. National Clinical Guidelines for the treatment of HCV in adults version 3.0, January 2017.

This assessment is based on data submitted by the applicant company up to and including 14 August 2017.

**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

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.