Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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sofosbuvir 400mg tablet (Sovaldi®) SMC No. (964/14)

Gilead Sciences Ltd.

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

ADVICE: following a full submission

sofosbuvir (Sovaldi®) is accepted for restricted use within NHS Scotland.

Indication under review: in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

SMC restriction: Sofosbuvir is accepted for use in patients with genotypes 1 to 6. Use in treatment-naive patients with genotype 2 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa. Use of the 24-week interferon-free regimen of sofosbuvir in combination with ribavirin in patients with genotype 3 is restricted to those who are ineligible for, or are unable to tolerate, peginterferon alfa.

Sofosbuvir in combination with ribavirin, or peginterferon plus ribavirin, produced sustained virological suppression in patients with all genotypes of hepatitis C. It is the first medicine licensed for use in interferon-free regimens and may be associated with improved tolerability compared to standard interferon-based regimens.

No clinical or economic data were presented for treatment-experienced patients with genotype 1.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

In combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults.

Dosing Information

400 mg tablet, taken orally, once daily with food. Sofosbuvir should be used in combination with other medicinal products. Monotherapy of sofosbuvir is not recommended.

Sofosbuvir in combination with ribavirin and peginterferon alfa for 12 weeks is suitable for patients with genotype 1, 3, 4, 5 or 6.

Sofosbuvir in combination with ribavirin can be given for 24 weeks to patients with genotype 3 and to those with genotype 1, 4, 5 or 6 who are ineligible for or do not tolerate peginterferon alfa; for 12 weeks to patients with genotype 2 and; until transplant, in patients awaiting transplant with duration of therapy in patients awaiting transplant guided by an assessment of the potential benefits and risks for the individual patient.

For the 12-week regimens, consideration should be given to extending the duration of therapy beyond 12 weeks and up to 24 weeks; especially for those subgroups who have one or more factors historically associated with lower response rates to interferon-based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentration, black race, IL28B non CC genotype, prior null response to peginterferon alfa and ribavirin therapy)

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

Product availability date

January 2014

Summary of evidence on comparative efficacy

Sofosbuvir, a nucleotide prodrug, is the first medicine in a new class that inhibits the hepatitis C virus NS5B RNA polymerase, which is essential for viral replication. It can be used to treat all genotypes (1 to 6) and must be given in combination with ribavirin or peginterferon plus ribavirin.[1,2] It is the third direct acting antiviral (DAA) drug marketed in the UK for chronic hepatitis C. The other two, telaprevir and boceprevir, are only indicated for treatment of genotype 1 and have been accepted for use by SMC within their licensed indications.[3,4]

Four phase III studies recruited adults with chronic hepatitis C infection genotype 2 or 3 (FISSION, FUSION, POSITRON and VALENCE). The FISSION study randomised treatment-naïve patients equally, with stratification for genotype (2 or 3), HCV RNA (<6 log10 IU/mL or ≥6 log10 IU/mL) and cirrhosis (presence or absence) to open-label sofosbuvir 400mg once daily plus weight-based ribavirin (1000mg or 1200mg for body weight <75kg and >75kg, respectively) for 12 weeks or peginterferon alfa-2a 180microgram subcutaneously (sc) once weekly and ribavirin (400mg twice daily) for 24 weeks. In the POSITRON study, patients intolerant of,

unwilling or ineligible for treatment with interferon were randomised in a 3:1 ratio, with stratification for cirrhosis (presence or absence), to double-blind sofosbuvir 400mg once daily plus weight-based ribavirin or placebo for 12 weeks. In the FUSION study, patients who had prior treatment failure with interferon were equally randomised, with stratification for genotype (2 or 3) and cirrhosis (presence or absence), to double-blind sofosbuvir 400mg once daily plus weight-based ribavirin for 12 weeks followed by placebo for 4 weeks or to sofosbuvir 400mg once daily plus weight-based ribavirin for 16 weeks. The VALENCE study, which included treatment-naïve and -experienced patients, was initially a randomised comparison of sofosbuvir 400mg once daily plus weight-based ribavirin for 12 weeks to placebo. However, following review of data from the FUSION study it was unblinded before completion. Patients in the placebo group were offered treatment in a separate study and those with genotype 3 who had not completed treatment had their course extended to 24 weeks, while those with genotype 2 remained on 12 weeks therapy. In all studies, the primary outcome was sustained virological response (SVR), defined as HCV RNA levels below lower limit of quantification (LLOQ), 12 weeks after end of treatment (SVR12). FISSION was a non-inferiority study, with a pre-specified margin of 15%. The primary analysis assessed superiority relative to placebo in the POSITRON study and relative to a historical control of 25% in the FUSION study. Data from the VALENCE study were descriptive only.[1,2,5-15]

In the FISSION study, non-inferiority of sofosbuvir plus ribavirin to peginterferon plus ribavirin was demonstrated, with a between treatment difference of 0.3% (95% confidence interval (CI): -7.5% to 8.05). SVR12 was achieved by statistically significantly more patients given sofosbuvir plus ribavirin compared with placebo in POSITRON study and compared with a historical control rate of 25% in the FUSION study. In the latter study, SVR12 rate was statistically significantly greater with sofosbuvir plus ribavirin for 16 weeks versus 12 weeks, with a between group difference of -22% (95% CI: -35% to -9%). Results are detailed in table 1.[1,2,5-15]

Table 1: Subgroup analysis of SVR12 by genotype and presence of cirrhosis.[1,2,5-15]

	Treatment	Overall	No cirrhosis	Cirrhosis
FISSION: treatment-naïve				
All patients	SOF + RBV 12wks	67% (171/256)	72% (148/206)	46% (23/50)
	PEG + RBV 24wks	67% (162/243)	74% (143/193)	38% (19/50)
Genotype 2	SOF + RBV 12wks	94% (69/73)	97% (59/61)	83% (10/12)
	PEG + RBV 24wks	78% (52/67)	82% (44/54)	62% (8/13)
Genotype 3	SOF + RBV 12wks	56% (102/183)	61% (89/145)	34% (13/38)
	PEG + RBV 24wks	62% (110/176)	71% (99/139)	30% (11/37)
POSITRON: intolerant of, unwilling or ineligible for interferon				
All patients	SOF + RBV 12wks	78% (161/207)	81% (142/176)	61% (19/31)
Genotype 2	SOF + RBV 12wks	93% (101/109)	92% (85/92)	94% (16/17)
Genotype 3	SOF + RBV 12wks	61% (60/98)	68% (57/84)	21% (3/14)
FUSION: treatment-experienced (failed previous interferon treatment)				
All patients	SOF + RBV 12wks	50% (51/103)	60% (40/67)	31% (11/36)
	SOF + RBV 16wks	71% (70/98)	74% (49/66)	66% (21/32)
Genotype 2	SOF + RBV 12wks	82% (32/39)	90% (26/29)	60% (6/10)
	SOF + RBV 16wks	89% (31/35)	92% (24/26)	78% (7/9)
Genotype 3	SOF + RBV 12wks	30% (19/64)	37% (14/38)	19% (5/26)
	SOF + RBV 16wks	62% (39/63)	62% (25/40)	61% (14/23)

VALENCE: treatment-naïve and treatment-experienced				
Genotype 2[N]	SOF + RBV 12wks	97% (31/32)	97% (29/30)	100% (2/2)
Genotype 2[E]	SOF + RBV 12wks	90% (37/41)	91% (30/33)	88% (7/8)
Genotype 3[N+E]	SOF + RBV 12wks	27% (3/11)	33% (3/9)	0% (0/2)
Genotype 3[N]	SOF + RBV 24wks	93% (98/105)	94% (86/92)	92% (12/13)
Genotype 3[E]	SOF + RBV 24wks	77% (112/145)	85% (85/100)	60% (27/45)

SOF = sofosbuvir; RBV = ribavirin; PEG = peginterferon alfa-2a; SVR12 = sustained virological response at 12 weeks post-end of treatment. N = treatment-naïve; E= treatment-experienced.

In an open-label study (NEUTRINO), 327 treatment-naïve adults with genotype 1, 4, 5 or 6 chronic hepatitis C received sofosbuvir 400mg once daily, peginterferon-alfa-2a 180micrograms sc weekly and weight-based ribavirin for 12 weeks. The primary endpoint was SVR12 and superiority was demonstrated relative to an adjusted historical control rate of 60%, with 296/327 (91%: 95% CI: 87% to 93%) patients achieving SVR12. Rates were 93% (253/273) and 80% (43/54) in patients without cirrhosis and with cirrhosis, respectively. SVR12 rates by genotype were 92% (206/225) for 1a; 83% (55/66) for 1b; 96% (27/28) for 4; 100% (1/1) for 5 and 100% (6/6) for 6.[1,2,5,6,16,17]

In the FISSION, POSITRON, FUSION and NEUTRINO studies, all virological failures within the sofosbuvir plus ribavirin groups were relapses, except one patient with virological breakthrough on treatment who had pharmacokinetic parameters compatible with non-compliance. In the sofosbuvir groups, samples taken at relapse from patients who relapsed after SVR at end of treatment showed no resistance-associated variants in sequencing analysis.[2,5-17]

In an ongoing, open-label study (PHOTON-1), 223 adults with genotype 1, 2 or 3 hepatitis C and HIV received sofosbuvir 400mg once daily plus weight-based ribavirin for 24 weeks or, if they were treatment-naïve and had genotype 2 or 3, for 12 weeks. At an interim analysis, all treatment-naïve patients and 28 of 41 treatment-experienced patients with genotype 2 or 3 had follow-up for the primary endpoint, SVR12, and these data are summarised in table 2. All virological failures were relapses, except two patients with on-treatment virological failure, who had evidence of non-adherence.[2,8,17,18]

Table 2: PHOTON-1 interim analysis data

Patient group	Treatment	SVR12	On-Rx failure	Relapse	Other
Genotype 1[N]	SOF + RBV 24wks	76% (87/114)	1/114 (0.9%)	25/113 (22%)	1/114 (0.9%)
Genotype 2[N]	SOF + RBV 12wks	89% (23/26)	1/68 (1.5%)	12/67 (18%)	4/68 (5.9%)
Genotype 3[N]	SOF + RBV 12wks	67% (28/42)			
Genotype 2[E]	SOF + RBV 24wks	93% (14/15)	0/28	2/28 (7.1%)	0/28
Genotype 3[E]	SOF + RBV 24wks	92% (12/13)			

SOF = sofosbuvir; RBV = ribavirin; SVR12 = sustained virological response at 12 weeks post-end of treatment. N = treatment-naïve; E= treatment-experienced. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment. Other includes patients who did not meet criteria for SVR12 or criteria for virological failure.

In another ongoing, open-label study (P7977-2025), 61 adults with hepatitis C genotypes 1 to 4 and hepatocellular carcinoma awaiting liver transplant received sofosbuvir 400mg once daily plus weight-based ribavirin for 24 weeks, prior to a protocol amendment extending treatment to 48 weeks, or until transplant (whichever occurred first). The primary endpoint was virological

suppression 12 weeks post-transplant. At an interim analysis, this was achieved by 62% (23/37) of patients who underwent transplant, had HCV-RNA <LLOQ at the time of transplant and reached 12 weeks post-transplant. Of the 14 patients who had HCV-RNA <LLOQ at transplant but did not reach the primary endpoint, 10 had recurrence of HCV, 3 died within 14 days post-transplant and 1 withdrew consent with HCV<LLOQ.[2,8,19,20]

Numerous smaller studies support the efficacy of sofosbuvir.[21-29] The QUANTUM and SPARE studies provide additional data on sofosbuvir plus ribavirin for 12 weeks in treatment-naïve patients with genotype 1, with SVR12 of 66% (69/105) and SVR24 of 68% (17/25) in the respective studies. The phase II studies, ELECTRON, PROTON and LONESTAR-2, provide the only clinical data in genotype 3 for sofosbuvir plus peginterferon and ribavirin for 12 weeks, with SVR12 rates of 97% (38/39) in treatment-naïve patients (ELECTRON and PROTON combined) and 83% (20/24) in treatment-experienced patients (LONESTAR-2).

Summary of evidence on comparative safety

The adverse event profile of sofosbuvir plus ribavirin is consistent with that of ribavirin, and the adverse events associated with sofosbuvir in combination with pegylated interferon and ribavirin are similar to those with pegylated interferon plus ribavirin regimens. The known adverse effects of ribavirin and pegylated interferon use do not seem to worsen when used in combination with sofosbuvir. No clustering of adverse events and no trends in any specific adverse event type were noted in the review of safety data from sofosbuvir studies.[2,5]

In the FISSION study, sofosbuvir plus ribavirin for 12 weeks, compared with pegylated interferon plus ribavirin for 24 weeks, was associated with decreased rates of adverse events (86% versus 96%); treatment-related adverse events (72% versus 94%); grade 3 or 4 adverse events (6.6% versus 19%); treatment-related grade 3 or 4 adverse events (3.1% versus 16%); adverse events leading to discontinuation of study drug (1.2% versus 12%); adverse events leading to interruption of study drug (10% versus 27%). The incidence of adverse events within the various organ systems was consistently lower in the sofosbuvir plus ribavirin group. The most common in both study groups were fatigue, headache, nausea and insomnia. With the exception of dizziness and anaemia, all events occurring in at least 10% of patients were more common among patients receiving peginterferon than sofosbuvir. Similar adverse event profiles were observed with sofosbuvir plus ribavirin regimens in the POSITRON and FUSION studies, which were greater than those with placebo, in the POSITRON study.[2,5-13]

Summary of clinical effectiveness issues

Treatment of chronic hepatitis C infection aims at eradicating virus and consequently preventing cirrhosis and its complications, reducing extra-hepatic manifestations and preventing infection of other people. In Scotland, the majority of patients with hepatitis C virus have genotype 1 or 3 infection (49% and 46% respectively) and the remainder genotypes 2, 4 or 5.[33]

Sofosbuvir is the first medicine in a new class that inhibits the hepatitis C virus NS5B RNA polymerase. It can be used for all six genotypes of chronic hepatitis C. It is the first medicine that can be used in regimens not containing an interferon. Sofosbuvir plus ribavirin is licensed for use in genotypes 2 or 3 and, in those unable to receive interferon, for genotypes 1, 4, 5 or 6.[1,2] This addresses an unmet need, as many patients are unable to receive the standard

peginterferon plus ribavirin treatment due to intolerance to the considerable adverse effects associated with interferon. In addition, there are some patients who do not respond to current therapies. The European Medicines Agency (EMA) also noted that the potential to use sofosbuvir plus ribavirin therapy to prevent graft infection (and/or obtain SVR) in patients on the liver transplant list marks an important therapeutic improvement.[2]

In genotype 1, there are no direct comparative data versus standard treatment with peginterferon plus ribavirin in combination with telaprevir or boceprevir. Most patients (89%) in the NEUTRINO study had genotype 1. This study did not contain a control group. It primarily assessed efficacy relative to a historical control rate of 60%, which was derived from pivotal studies supporting licensed indications of telaprevir (ADVANCE study)[30] and boceprevir (SPRINT-2 study)[31]. In the whole study population and those with genotype 1, the primary outcome was achieved with 12-week sofosbuvir, peginterferon plus ribavirin regimen by the majority of patients (91%) and this was significantly greater than the historical control rate.[2]

In genotype 1 patients who are not suitable for treatment with interferon, use of a 24-week regimen of sofosbuvir plus ribavirin is supported by data from the PHOTON-1, QUANTUM and SPARE studies. In the respective studies SVR12 (SVR24 in SPARE) was achieved by 76%, 66% and 68% of patients.[2,5,17,18,21-23]

In genotype 2 treatment-naïve patients, sofosbuvir plus ribavirin for 12 weeks, compared to 24 weeks of peginterferon plus ribavirin, was associated with significantly greater SVR12: 94% versus 78% (in the FISSION study). A similar SVR12 rate of 93% was seen with 12 weeks of sofosbuvir plus ribavirin in patients who could not receive interferon (in the POSITRON study). In patients who previously failed on an interferon regimen, extending treatment with sofosbuvir plus ribavirin from 12 weeks to 16 weeks increased SVR12 from 82% to 89% (in the FUSION study). In the VALENCE study, 12 weeks of sofosbuvir plus ribavirin resulted in SVR12 rates of 97% and 90% in treatment-naïve and -experienced patients, respectively.[2,5-15]

There are fewer data supporting the interferon-free licensed regimen for genotype 3 (sofosbuvir and ribavirin for 24 weeks). In the VALENCE study this was associated with SVR12 rates of 93% and 77% in treatment-naïve and -experienced patients, respectively. The main clinical studies FISSION, POSITRON and FUSION found the 12-week regimen produced SVR12 rates of 56%, 61% and 30% in the respective studies, with the latter demonstrating a rate of 62% with a 16-week regimen. The only clinical data for the other regimen licensed for use in genotype 3 (sofosbuvir, peginterferon and ribavirin for 12 weeks) are from small studies. SVR12 rates of 97% (38/39) were observed in treatment-naïve patients (ELECTRON and PROTON combined) and 83% (20/24) in treatment-experienced patients (LONESTAR-2). However, the European regulatory authority noted that efficacy of this regimen, which is the same as the regimen used in the NEUTRINO study in mainly genotype 1 patients, may be extrapolated to genotype 3 based on the higher efficacy of peginterferon and ribavirin against genotype 3 compared to genotype 1 and the similar effect of sofosbuvir against both genotypes. [2,5-15]

Clinical data in genotypes 4, 5 and 6, which are uncommon in Europe, are limited and the European regulatory authority notes that a totality of evidence approach to demonstrate efficacy was used for these. Outcomes in the few patients treated are similar to those seen in genotype 1, with an SVR rate of 97% (34/35) in patients treated within the NEUTRINO study.[2,5,7,16]

There are no clinical data for sofosbuvir in treatment-experienced patients with genotypes 1, 4, 5 or 6. Both the European and US regulatory authorities note a similar point in relation to efficacy in this group. That is, about 50% of patients in a treatment-naïve population will

become non-responders to peginterferon plus ribavirin, i.e. treatment-experienced. As peginterferon plus ribavirin is an immune therapy that does not select for viral resistance, these patients will have unchanged susceptibility to antivirals and can be considered to be functionally represented in the treatment-naïve population. Thus the high SVR12 rate in the NEUTRINO study in treatment-naïve patients supports effectiveness of the sofosbuvir regimen in treatment-experienced patients.[2,5]

The sofosbuvir-containing regimens and treatment durations vary across genotypic subgroup and the relevant comparators also vary depending on previous treatment and response to it. This produces a complex range of comparative treatment options. There are no direct comparative data for licensed sofosbuvir-containing regimens with current standard treatments, except for the subset of genotype 2 patients in the FISSION study, which compared 12 weeks of sofosbuvir plus ribavirin with 24 weeks of peginterferon and ribavirin. The submitting company performed a literature search to assess the feasibility of a mixed treatment comparison and concluded that the available data would not provide a robust comparison. Therefore, data from the individual studies were input to the economic models, effectively creating naïve indirect comparisons.

Clinical experts consulted by SMC considered that sofosbuvir is a therapeutic advancement due to improved efficacy and tolerability across all genotypes relative to existing treatment options. Sofosbuvir is used in simple regimens with no requirement for response-guided therapy (in contrast to the other direct acting antivirals, telaprevir and bocaprevir). The sofosbuvir plus ribavirin regimens include only oral medicines and this may be more acceptable to patients than regimens that include peginterferon administered subcutaneously. Clinical experts advised that the place in therapy of sofosbuvir would be dependent on the genotype and patient characteristics. In general, they suggested use in combination with peginterferon and ribavirin for genotypes 1 and 3. They also noted that some patients are awaiting the advent of newer therapies with fewer side-effects; therefore, the introduction of sofosbuvir may result in increased demand on the service.

Addition of sofosbuvir to ribavirin or peginterferon plus ribavirin does not appear to increase the adverse events associated with these. In the FISSION study, sofosbuvir, peginterferon and ribavirin for 12 weeks was associated with improved tolerability relative to peginterferon plus ribavirin for 24 weeks. Interferon is associated with a significant adverse effect profile, which can limit its use in practice. In general, sofosbuvir is interferon-sparing (either enabling interferon-free regimens or reducing the duration of interferon-based regimens) and it may be associated with improved tolerability, although direct comparative clinical data to verify this are not available.

Summary of comparative health economic evidence

The submitting company presented a lifetime cost-utility analysis comparing various sofosbuvir regimens in different patient populations according to genotype, previous treatments and suitability for interferon treatment. This meant that base case cost-effectiveness ratios were presented for 18 different scenarios and 5 supplementary results for patients co-infected with HIV. The comparator for each scenario varied accordingly. For all analyses where patients were deemed unsuitable for interferon, the comparison was against no treatment, which seemed appropriate. For genotype 1 groups eligible for interferon, comparisons were made against regimens containing peginterferon and ribavirin, telaprevir or boceprevir. For treatment-

naive genotype 2 and 3 patients eligible for treatment with interferon, comparison was made against regimens containing pegylated interferon and ribavirin given for 24 weeks; for treatment-experienced patients of these genotypes, the comparison was against peginterferon and ribavirin given for 48 weeks. For genotypes 4, 5 and 6, the comparator was also a 48 week regimen of peginterferon and ribavirin.

For each of the scenarios considered, a common Markov modelling structure was used based on an existing published model. The model covered states for SVR (assumed to have permanently cleared virus), non-cirrhotic, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and post- liver transplant. Age and gender specific mortality rates were also applied to each state of the model. The modelling structure did not differentiate between mild and moderate disease among non-cirrhotic patients, as has been seen in other economic models. Patients were assumed to be aged 40 to 45 at the start of the model.

Clinical data on SVR rates from the various studies described above were inputted to the model according to the particular patient group of interest. In all of the comparisons versus active treatment with the exception of genotype 2, treatment-naïve, interferon-eligible patients, there were no directly comparative clinical studies so naive indirect comparisons were used, and in some cases SVR rates for sofosbuvir from different studies combined by simple addition, to give an overall SVR rate. In the comparisons for the interferon-unsuitable patients, in some cases the company made an assumption that the SVR for no treatment was zero, which seems broadly acceptable. The transition probabilities for the longer term states of the model were common between treatment and comparator regimens and taken from published sources; this means that the key drivers of the model were the initial SVR rates from the clinical studies. Assumptions had to be made in terms of transitioning patients from the non-cirrhosis state to compensated cirrhosis because the source paper reported data according to mild, moderate and cirrhotic stages of the disease. It is quite challenging to critique the method used but what should be noted is that the sensitivity analysis shows that the results for some subgroups can be sensitive to the resulting values used for transition probabilities.

Utility values on treatment for sofosbuvir were estimated from trial data, and for other health states in the model taken from literature sources. The base case utility value for a non-cirrhotic patient was 0.74, and 0.55 for a patient with compensated cirrhosis. A key utility value was an assumed 0.05 increment for patients experiencing an SVR based on a published study. This assumption has also been used in other recent SMC submissions.

Health state costs were largely taken from published sources and are similar to health state costs used in previous submissions to SMC. Monitoring costs for sofobuvir were lower against the other active comparators.

The base case cost per quality adjusted life year (QALY) results for the 18 scenarios are shown in the table below:

Patient group	Sofosbuvir regimen	Comparator			
		No treatment	PEG IFN2a/RBV	Telaprevir	Boceprevir
GT1					
TN IFN eligible	SOF/PEG/RBV 12week	-	£15,351	£12,167	£7,539
TN unsuitable for IFN	SOF/RBV 24week	£50,973	-	-	-
GT2					
TN IFN eligible	SOF/RBV 12week	-	£48,051	-	-
TN unsuitable for IFN		£8,593	-	-	-
TE IFN eligible		£9,751	£13,198	-	-
TE unsuitable for IFN		£9,045	-	-	-
GT3					
TN IFN eligible	SOF/PEG/RBV 12 week	-	£21,372	-	-
	Alternative: SOF/RBV 24week		*£48,280*	-	
TN unsuitable for IFN	SOF/RBV 24week	£22,324	-	-	-
TE IFN eligible	SOF/PEG/RBV 12 week	£8,961	£12,842	-	-
	Alternative: SOF/RBV 24week	*£29,500*	*£50,605*	-	-
TE unsuitable for IFN	SOF/RBV 24week	£29,642	-	-	-
GT4/5/6					
TN	SOF/PEG/RBV 12 week	-	£27,981	-	-

IFN, interferon; PEG IFN2a, pegylated interferon 2a; RBV, ribavirin; TE, treatment-experienced; TN, treatment-naïve

For the HIV co-infected patients, the incremental cost effectiveness ratio (ICER) ranged from being dominated (less effective, more expensive) in genotype 3 treatment-naive patients and upwards of £100k per QALY in genotype 2 and 3 treatment-experienced patients versus active treatment with peginterferon and ribavirin. Only in the analysis for genotype 2 and 3 treatment-experienced patients versus no treatment were the ICERs below £20k: £11, 081 per QALY for genotype 2 patients and £11,156 for genotype 3 patients. These figures were based on data from the PHOTON study; however, the company has indicated that the ICERS for the mono-infected population should be taken as representative of the ICERs in the co-infected patients.

A range of one way sensitivity analyses was provided for each of the 18 base case cost per QALY estimates in addition to helpful probabilistic sensitivity analysis and threshold analysis on the key SVR statistics. Given the number of base case ICERs presented above and the various types of sensitivity analysis presented for each, reporting all the sensitivity analysis would be

difficult in this summary. Relevant pieces of key sensitivity analysis are noted below for base case ICERs that were above levels of cost effectiveness which would generally be considered less cost-effective (i.e. in the £20k to £30k range and above).

Genotype 1/ treatment naive/ IFN unsuitable (base case £50,973)

- Transition probability non-cirrhotic to compensated cirrhosis for patients aged 40- £72k when reduced to 0.0025 from a base case of 0.001
- Recurrence and re-infection- £56,626 when these are re-introduced to the model

Genotype 2/ treatment naive/ IFN eligible (base case £48,051)

- SVR comparator cirrhotic- £80,755 (if 84.9% rather than base case of 61.5%, important given naive indirect comparison)
- SVR 12 sofosbuvir- £78,167 (response of 64% rather than base case of 85.7%, note naive indirect comparison)
- Transition probability non cirrhotic to compensated cirrhosis (range as above)- £62,236

Genotype 3/ treatment naive/ IFN unsuitable (base case £22,324)

- Transition probability non cirrhotic to compensated cirrhosis (range as above)- £31,117

Genotype 3/ treatment naive/ IFN eligible 12 weeks of SOF (base case £21,372)

- SVR sofosbuvir 12 weeks- £31,605 if reduced from 83% to 59%

Genotype 3/ treatment naive/ IFN eligible 24 weeks of SOF (base case £48, 280)

- SVR sofosbuvir 12 weeks- £53,416 if reduced to 87.6% from base case of 93.5%
- SVR comparator 24 weeks- £58,512 if increased from 29.7% to 45.2% (again important given naive comparison)

Genotype 3/ treatment experienced/ IFN unsuitable (base case £29,642)

- Transition probability non- cirrhotic to compensated cirrhosis (range as above) - £42,698

Genotype 3/ treatment experienced/ IFN eligible SOF 24 weeks versus no treatment (base case £30k)

- Transition probability non cirrhotic to compensated (range as above) - £42,391

Genotype 3/ treatment experienced/ IFN eligible SOF 24 weeks versus PEG IFN (base case £50,605)

- Transition probability non-cirrhotic to compensated (range as above)- £71,463

Genotypes 4/ 5/ 6 treatment naive (base case £27,981)

- SVR12 sofosbuvir - £45,578 if reduced from 100% to 80% (important given naive indirect comparison on small number of patients)
- SVR 24 comparator - £48,840 if increased from 50% to 73.4% (again note indirect comparison)

In terms of the SVR rates, these are important findings given the points raised above regarding the weaknesses in evaluating comparative efficacy (subgroup analysis on small patient numbers, naive indirect comparisons, summing SVRs across different studies). The results where naive indirect comparisons have been used against active comparators all show that the SVRs are variables that are important to the results.

In terms of the sensitivity to the transition probability from non-cirrhotic to compensated cirrhosis, as noted above, the base case value was derived using published data and a range of assumptions which are difficult to critique. However, the company has indicated that the assumptions they used had been validated with experts in the field and thus were reasonable. The resulting QALY gains were also said to be consistent with results seen in models which used different assumptions for these transition probabilities.

For the ICERs that were in the lower range below £20k per QALY, a key parameter was the SVR rates and the company's threshold analyses were useful in providing reassurance that the SVR rates for sofosbuvir would often have to fall considerably for the treatment to no longer be seen as cost-effective, and in addition, probabilistic analysis demonstrated very high likelihoods of cost-effectiveness for these groups.

As noted, there were limitations associated with the evidence based used in the economic analysis. In many cases, the cost-effectiveness ratios were judged to be cost-effective and the sensitivity analysis provided reassurance around key statistics such as SVR rates. For some of the groups presented, the cost-effectiveness ratios were particularly high and SMC judged that the economic case had not been demonstrated. However, in the case of the genotype 1 patients who were treatment naive and unsuitable for interferon-based treatments, SMC considered the benefits of sofosbuvir in the context of the SMC decision modifiers and agreed that the criterion for an absence of other treatment options was satisfied. As such, the committee agreed that the relatively high cost per QALY was acceptable for this group given the expected benefits of the treatment and in the context of this decision modifier.

Summary of patient and public involvement

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

- Submissions were received from Hepatitis Scotland, Waverley Care and The Hepatitis C Trust, all registered charities.

- All three charities have received funding from several pharmaceutical companies in the past two years.

- Hepatitis C is a blood-borne virus that can result in inflammation and significant damage to the liver, affecting its ability to perform essential functions. Research has shown that the hepatitis C virus (HCV) can affect a number of other areas of the body including the digestive, lymphatic and immune systems, and the brain.

- Patients living with the disease can be seriously debilitated and may not be able to work, and some have lost their jobs when they have revealed their HCV status. Living with HCV is often a challenge which impacts on family, carers and the patient.

- Current treatments can be lengthy, may have difficult to tolerate side effects and aren't recommended for those with advanced liver disease or awaiting a liver transplant.

- Sofosbuvir can have a reduced treatment duration, potentially improved side effect profile and is more easily tolerated but the potentially large costs of the drug were commented on.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline number 133, management of hepatitis C, was published in July 2013. This recommends that treatment-naïve and treatment-experienced patients infected with hepatitis C genotype 1 should be considered for treatment with pegylated interferon and weight based ribavirin with the addition of a protease inhibitor as triple therapy. Response-guided therapy can only be used in treatment-naïve patients and previous treatment relapsers who are not cirrhotic. For patients with hepatitis C genotype 2 or 3 standard treatment should be pegylated interferon and weight based ribavirin for 24 weeks. Non-cirrhotic patients, with genotype 2 or 3, who achieve a rapid viral response at week 4 of therapy, could be considered for shortened duration of therapy of 12 to 16 weeks. For patients with hepatitis C genotype 4, 5 or 6 infection, standard treatment should be 48 weeks of pegylated interferon and weight based ribavirin. Patients co-infected with HIV and hepatitis C genotype 1 should be considered for treatment with a regimen that includes a hepatitis C virus protease inhibitor. Treatment-naïve patients with HIV and hepatitis C genotype 1 who are unsuitable for this regimen should be considered for treatment with pegylated interferon and weight based ribavirin for 48 to 72 weeks depending on viral response. For patients co-infected with HIV and hepatitis C genotype 1 who do not achieve an early virological response, treatment should be stopped. Patients with HIV and hepatitis C non-genotype 1 who are considered suitable for treatment, should be offered pegylated interferon and weight-based ribavirin for 48 weeks. Patients with HIV and hepatitis C genotype 2 or 3 who achieve a rapid virological response may be considered for 24 weeks of treatment. Patients co-infected with hepatitis B and C should be considered for treatment with pegylated interferon and weight-based ribavirin.[32]

Additional information: comparators

The standard treatment for genotype 1 is peginterferon and weight-based ribavirin plus a protease inhibitor, telaprevir or bocaprevir, with response-guided therapy determining treatment duration in certain groups, which ranges from 24 to 48 weeks. Genotype 2 or 3 is generally treated with peginterferon and weight-based ribavirin for 24 to 48 weeks, although non-cirrhotic patients who achieve a rapid viral response can receive shorter courses of 12 to 16 weeks. For patients with genotype 4, 5 or 6 infection, standard treatment is 48 weeks of peginterferon and weight-based ribavirin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Genotype 1		
Sofosbuvir Peginterferon-alfa-2a Ribavirin	**400mg once daily for 12 to 24 weeks 180mcg once weekly for 12 to 24 weeks 1000mg to 1200mg daily for 12 to 24 weeks**	**37,400 to 74,801**
Sofosbuvir* Ribavirin	**400mg once daily for 24 weeks 1000mg to 1200mg daily for 24 weeks**	**71,816**
Boceprevir Peginterferon-alfa-2b	800mg three times daily for 24 to 48 weeks 1.5mcg/kg once weekly for 28 to 48 weeks	22,397 to 43,194

Ribavirin	800mg to 1800mg for 28 to 48 weeks	
Telaprevir Peginterferon-alfa-2a Ribavirin	2250mg daily in divided doses for 12 weeks 180mcg once weekly for 24 to 48 weeks 1000mg to 1200mg daily for 24 to 48 weeks	27,234 to 32,069
Peginterferon-alfa-2a Ribavirin	180mcg once weekly for 24 to 48 weeks 1000mg to 1200mg daily for 24 to 48 weeks	4,836 to 9,672
Peginterferon-alfa-2b Ribavirin	1.5mcg/kg once weekly for 24 to 48 weeks 800mg to 1800mg daily for 24 to 48 weeks	4,797 to 9,594
Genotype 2		
Sofosbuvir Ribavirin	**400mg once daily for 12 to 24 weeks 1000mg to 1200mg daily for 12 to 24 weeks**	**35,908 to 71,816**
Peginterferon-alfa-2a Ribavirin	180mcg once weekly for 16 to 48 weeks 1000mg to 1200mg daily for 16 to 48 weeks	2,977 to 9,672
Peginterferon-alfa-2b Ribavirin	1.5mcg/kg once weekly for 24 to 48 weeks 800mg to 1800mg daily for 24 to 48 weeks	4,797 to 9,594
Genotype 3		
Sofosbuvir Peginterferon-alfa-2a Ribavirin	**400mg once daily for 12 to 24 weeks 180mcg once weekly for 12 to 24 weeks 1000mg to 1200mg daily for 12 to 24 weeks**	**37,400 to 74,801**
Sofosbuvir* Ribavirin	**400mg once daily for 24 weeks 1000mg to 1200mg daily for 24 weeks**	**71,816**
Peginterferon-alfa-2a Ribavirin	180mcg once weekly for 16 to 48 weeks 1000mg to 1200mg daily for 16 to 48 weeks	2,977 to 9,672
Peginterferon-alfa-2b Ribavirin	1.5mcg/kg once weekly for 24 to 48 weeks 800mg to 1800mg daily for 24 to 48 weeks	4,797 to 9,594
Genotype 4,5,6		
Sofosbuvir Peginterferon-alfa-2a Ribavirin	**400mg once daily for 12 to 24 weeks 180mcg once weekly for 12 to 24 weeks 1000mg to 1200mg daily for 12 to 24 weeks**	**37,400 to 74,801**
Sofosbuvir* Ribavirin	**400mg once daily for 24 weeks 1000mg to 1200mg daily for 24 weeks**	**71,816**
Peginterferon-alfa-2a** Ribavirin	180mcg once weekly for 24 to 48 weeks 1000mg to 1200mg daily for 24 to 48 weeks	4,836 to 9,672
Peginterferon-alfa-2b*** Ribavirin	1.5mcg/kg once weekly for 24 to 48 weeks 800mg to 1800mg daily for 24 to 48 weeks	4,797 to 9,594

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 17 February 2014 and are based on a body weight of 70kg. The Copegus® brand of ribavirin is indicated for use in combination with peginterferon-alfa-2a and the Rebetol® brand of ribavirin is indicated for use in combination with peginterferon-alfa-2b. Peginterferon-alfa-2a was used in the pivotal studies of sofosbuvir and it is included in the other regimens for consistency. It is combined with ribavirin (Copegus®), weight based dosing of 1000mg if body weight <75kg and 1200mg, if body weight >75kg. An alternative treatment option is peginterferon-alfa-2b at a dose of 1.5microgram per kg once weekly, combined with ribavirin (Rebetol®) at a daily dose of 800mg, 1000mg, 1200mg or 1800mg, if body weight <65kg, 65-80kg, 81-105kg or >105kg, respectively.

* only suitable for patients with genotype 1,4,5 or 6 who are intolerant of or ineligible for treatment with peginterferon; **only 48 weeks treatment is recommended for genotypes 5 and 6; *** no recommendations within peginterferon SPC on dose/duration for treatment of genotype 5 or 6.

Additional information: budget impact

The submitting company presented a range of budget impact estimates according to patient genotype. For each, the company assumed that of the 37,600 patients with hepatitis C, 2.8% of patients would be eligible for some sort of treatment.

Genotypes 1 + 4-6
Of the eligible patients, 37.6% were estimated to be genotype 1, 4-6 patients and be treatment naive. To these figures, the company applied estimates of treatment uptake.

The company estimated net medicine budget impacts of £5.8m and £830k in years one and five respectively.

For the purpose of these calculations, it was assumed that 88% would receive 12 weeks of treatment with sofosbuvir and 12% would receive 24 weeks of treatment. For the calculation of displaced medicines costs, the company assumed that 36% of patients would be treatment-naive and hence receive telaprevir and peginterferon plus ribavirin, 16% would receive boceprevir, peginterferon and ribavirin, 35% would receive a 48 week regimen of peginterferon ribavirin and 12% would receive no treatment.

Genotype 2
Of the eligible patients, 1% were estimated to be genotype 2 patients. To these figures, the company applied estimates of treatment uptake.

The company estimated net medicines budget impacts of £249k and £93k in years one and five respectively.

For the purpose of the calculations presented for genotype 2 patients, it was assumed all would receive 12 weeks of treatment with sofosbuvir. For the calculation of displaced medicines costs, the company assumed that 65% of patients would receive peginterferon and ribavirin for 24 weeks, 22% would receive a 48 week regimen of peginterferon and ribavirin and 12% would receive no treatment.

Genotype 3:
Of the eligible patients, 46% were estimated to be genotype 3 patients. To these figures, the company applied estimates of treatment uptake.

The company estimated net medicines budget impacts of £13.6m and £5.1m in years one and five respectively.

For the purpose of the calculations presented for genotype 3 patients, it was assumed that 88% would receive 12 weeks of treatment with sofosbuvir and 12% would receive 24 weeks of treatment. For the calculation of displaced medicines costs, the company assumed that 65% of patients would be treatment naive and hence receive peginterferon and ribavirin for 24 weeks, 23% would be treatment experienced and therefore receive a 48 week regimen of peginterferon and ribavirin and 12% would receive no treatment.

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 11 April 2014.

**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.