Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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ledipasvir/sofosbuvir, 90mg/400mg, film-coated tablet (Harvoni®)

SMC No. (1030/15)

Gilead Sciences Ltd

06 February 2015

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

ledipasvir/sofosbuvir (Harvoni®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of chronic hepatitis C (CHC) in adults.

SMC restriction: genotype 1 and 4 CHC only.

In three, uncontrolled phase III studies conducted in treatment-naïve and treatment-experienced non-cirrhotic and cirrhotic patients with genotype 1 CHC, ledipasvir/sofosbuvir ± ribavirin achieved sustained virological response (at 12 weeks post treatment) rates of 93% to 99%, which were significantly superior to historical control rates.

No clinical or economic data were presented for genotype 3 patients with cirrhosis and/or prior treatment failure.

Overleaf is the detailed advice on this product.

Vice Chairman,
Scottish Medicines Consortium

Published 09 March 2015

Indication

Treatment of chronic hepatitis C (CHC) in adults.

Dosing Information

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

One tablet of ledipasvir/sofosbuvir 90mg/400mg once daily with or without food.

Genotype 1 and 4
Patients without cirrhosis: ledipasvir/sofosbuvir for 12 weeks (8 weeks may be considered in previously untreated genotype 1-infected patients and 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options).

Patients with compensated cirrhosis: ledipasvir/sofosbuvir for 24 weeks (12 weeks may be considered for patients deemed at low risk for clinical disease progression and who have subsequent retreatment options).

Patients with decompensated cirrhosis or who are pre-/post-liver transplant: ledipasvir/sofosbuvir + ribavirin for 24 weeks.
The daily dose of ribavirin is based on weight; <75kg (1,000mg) and ≥75kg (1,200mg) and administered orally in two divided doses with food.

Genotype 3
Patients with cirrhosis and/or prior treatment failure: ledipasvir/sofosbuvir + ribavirin for 24 weeks.

Product availability date

November 2014.

Summary of evidence on comparative efficacy

Ledipasvir/sofosbuvir is a fixed dose combination tablet comprising ledipasvir, a hepatitis C virus nonstructural protein 5A (HCV NS5A) replication complex inhibitor, and sofosbuvir, a pan-genotypic inhibitor of the HCV NS5B RNA-dependent RNA polymerase.[1] It was made available by the European Medicines Agency (EMA) for compassionate use (with or without ribavirin) in February 2014 for the treatment of adults infected with CHC genotype 1 virus, with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.[2] The marketing authorisation of ledipasvir/sofosbuvir is for treatment of chronic hepatitis C (CHC) in adults, and recommended treatment regimens for genotype 1, 3 and 4 CHC are included in the summary of product characteristics (SPC). The submitting company has requested that SMC considers ledipasvir/sofosbuvir when positioned for use in patients with genotype 1 and 4 CHC only.

Three open-label, uncontrolled phase III studies (ION-1, ION-2 and ION-3) have demonstrated efficacy of ledipasvir/sofosbuvir ± ribavirin in treatment naïve and treatment experienced patients with and without cirrhosis.[3-5] The studies recruited patients aged ≥18 years with CHC who had genotype 1 infection, a body mass index (BMI) ≥18kg/m^2 and HCV RNA ≥ 10^4 IU/mL at screening. In studies ION-1 and ION-3 patients were required to be treatment naive and in study ION-2 patients were treatment experienced, defined as treatment with peginterferon and ribavirin ± an NS3/4A protease inhibitor

which did not result in sustained virological response (SVR). Studies ION-1 and ION-2 could recruit up to 20% of patients with cirrhosis, defined as a Metavir stage F4, Ishak score of 5 or 6, Fibroscan score >12.5 kPa or a FibroTest® score >0.75 and an aspartate aminotransferase:platelet ratio index >2. Study ION-3 recruited non-cirrhotic patients only. Patients also had to satisfy defined laboratory parameters.

Patients were treated with ledipasvir/sofosbuvir 90mg/400mg orally once daily ± ribavirin orally twice daily (dose based on body weight; <75kg, 1,000mg/day and ≥75kg, 1,200mg/day). In ION-1 and ION-2 randomisation was stratified by HCV genotype 1 subtype (1a or 1b), the presence or absence of cirrhosis and, in ION-2, response to prior therapy (relapse or virologic breakthrough versus no response). In these studies patients were randomised to ledipasvir/sofosbuvir (12 weeks), ledipasvir/sofosbuvir + ribavirin (12 weeks), ledipasvir/sofosbuvir (24 weeks) or ledipasvir/sofosbuvir + ribavirin (24 weeks). ION-3 randomised patients (stratified by HCV genotype 1 subtype [1a or 1b]) to ledipasvir/sofosbuvir (8 weeks), ledipasvir/ sofosbuvir + ribavirin (8 weeks) or ledipasvir/sofosbuvir (12 weeks). [3-5]

The primary endpoint was SVR at 12 weeks post treatment (SVR12), defined as HCV RNA < lower limit of quantification, analysed in the full analysis set population, which comprised all randomised patients who received at least one dose of study drugs. All studies compared SVR12 in treatment arms to a historical control rate derived from phase III studies of telaprevir and boceprevir; 60% in ION-1 and ION-3 and 25% in ION-2. In addition, for study ION-3, the non-inferiority of treatment regimens was tested in a secondary analysis, using a non-inferiority margin of 12%. [3-5]

All treatment regimens were significantly superior to the historical control rates for SVR12. In study ION-3 the non-inferiority of treatment regimens was demonstrated. Results of the primary endpoint for ION-1 and ION-2 are presented in table 1 and for ION-3 in table 2.[3-5] High SVR12 response rates were observed across different patient subgroups including those with cirrhosis and genotype 1a CHC.

Table 1: Results of primary endpoint for studies ION-1 and ION-2 [3,5]

	ledipasvir/ sofosbuvir (12 weeks)	ledipasvir/ sofosbuvir + ribavirin (12 weeks)	ledipasvir/ sofosbuvir (24 weeks)	ledipasvir/ sofosbuvir + ribavirin (24 weeks)
ION-1; treatment naive patients				
N	214	217	217	217
SVR12; n (%; 95% CI)	211 (99%; 96% to 100%)	211 (97%; 94% to 99%)	212 (98%; 95% to 99%)	215 (99%; 97% to 100%)
p-value versus historical control SVR12 (60%)	p<0.001	p<0.001	p<0.001	p<0.001
ION-2; previously treated patients				
N	109	111	109	111
SVR12; n (%, 95% CI)	102 (94%; 87% to 97%)	107 (96%; 91% to 99%)	108 (99%; 95% to 100%)	110 (99%; 95% to 100%)
p-value versus historical control SVR12 (25%)	p<0.001	p<0.001	p<0.001	p<0.001

N=number of patients randomised; n=number of patients with SVR12; CI=confidence interval

Table 2: Results of primary endpoint for study ION-3 (treatment naive patients)[4]

	ledipasvir/ sofosbuvir (8 weeks)	ledipasvir/ sofosbuvir + ribavirin (8 weeks)	ledipasvir/ sofosbuvir (12 weeks)
N	215	216	216
SVR12; n (%; 95% CI)	202 (94%; 90% to 97%)	201 (93%; 89% to 96%)	206 (95%; 92% to 98%)
p-value versus historical control SVR12 (60%)	p<0.001	p<0.001	p<0.001
Difference (95% CI) versus ledipasvir/ sofosbuvir + ribavirin (8 weeks)	0.9% (-3.9% to 5.7%)	-	-
Difference (95% CI) versus ledipasvir/ sofosbuvir (12 weeks)	-1.4% (-6.4% to 3.6%)	-2.3% (-7.5% to 2.9%)	-

N=number of patients randomised; n=number of patients with SVR12; CI=confidence interval

Overall there were two virological failures on treatment (one each in ION-1 and ION-2); plasma levels of ledipasvir and the main sofosbuvir metabolite suggested that the patients were not complying with treatment. The total number of virological relapses after treatment was 36; ION-1 (n=2 [<1%]), ION-2 (n=11 [2.5%]) and ION-3 (n=23 [3.6%]). Most virological relapses occurred with the shorter treatment regimens; 8-week (n=20) and 12-week (n=15). [3-5]

A pooled analysis of quality of life data from ION-1, ION-2 and ION-3 studies has been published. The Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), Short Form-36 (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Work Productivity and Activity Index: Specific Health Problem (WPAI:SHP)] questionnaires were administered at baseline, during treatment and post treatment. There were significant increases compared to baseline (on a 0 to 100% normalised scale) in patient reported outcomes in the ledipasvir/sofosbuvir groups; 8 weeks (+7.4%), 12 weeks (+7.0%) and 24 weeks (+6.7%). Conversely there were decreases compared to baseline in patient reported outcomes in the ledipasvir/sofosbuvir + ribavirin groups; 8 weeks (up to -6.7%), 12 weeks (-6.3%) and 24 weeks (-4.9%). Using multivariate analysis the inclusion of ribavirin in treatment regimen was an independent predictor of patient reported outcome impairment. In patients who achieved sustained viral eradication there was a significant improvement in their patient reported outcomes; up to +8.3%.[6]

The pivotal studies excluded patients co-infected with human immunodeficiency virus (HIV). The open-label study, ERADICATE, was conducted in 50 treatment-naive (to HCV therapy), non-cirrhotic patients with genotype 1 CHC and co-infected with HIV. Patients were treated with ledipasvir/sofosbuvir for 12 weeks. The proportion of patients who were anti-retroviral (ARV) naive was 26% (13/50) and on treatment with ARV was 74% (37/50). In the ARV-naive group SVR12 was achieved in 100% (13/13) of patients and in patients on treatment with ARV, SVR12 was achieved 97% (36/37) of patients.[1,7,8]

SYNERGY, a single-centre, open-label, on-going, phase II study, provides some efficacy data in treatment naive and experienced patients with genotype 4 CHC.[9] Patients were treated with ledipasvir/sofosbuvir for 12 weeks. Of the 21 patients recruited 38% were treatment experienced and 43% had fibrosis stage 3 or 4. Data from an interim analysis are available for evaluable patients; 95% (19/20) of patients achieved an SVR12. In addition, the ION-1 study enrolled two patients with genotype 4d HCV infection and both achieved SVR12.[1]

Summary of evidence on comparative safety

At the time of submission to SMC there were no comparative safety data. Pooled safety analysis of 1,952 patients who were included in the ION studies is available; 1080 patients were treated with ledipasvir/sofosbuvir and 872 patients with ledipasvir/sofosbuvir + ribavirin.[10] Treatment-related adverse events occurred in 45% of patients treated without ribavirin and 71% of patients treated with ribavirin. Rates of treatment-related serious adverse events (≤0.4%) and treatment discontinuations due to adverse events (≤0.8%) were uncommon. Dose modifications or interruptions occurred in 0.6% of patients treated without ribavirin and 13.5% of patients treated with ribavirin. Treatment-related adverse events reported in >10% of patients in the ledipasvir/sofosbuvir versus ledipasvir/sofosbuvir + ribavirin pooled groups included fatigue (22% versus 38%), headache (21% versus 26%), nausea (10% versus 17%), insomnia (7.6% versus 18%), irritability (4.3% versus 11%), rash (4.4% versus 11%) and cough (3.8% versus 10%).[10]

Summary of clinical effectiveness issues

Following availability for compassionate use in February 2014, ledipasvir/sofosbuvir received marketing authorisation for treatment of chronic hepatitis C (CHC) in adults in November 2014 and recommended treatment regimens included in the SPC are for genotype 1, 3 and 4 CHC. The submitting company has requested that SMC considers ledipasvir/sofosbuvir when positioned for use in patients with genotype 1 and 4 CHC only. In Scotland of the people with CHC who had genotype testing, 48% had genotype 1, 46% had genotype 3 and 6% had other genotypes.[11]

Ledipasvir/sofosbuvir is the fourth peginterferon-free treatment licensed for genotype 1 and 4 CHC. While regimens containing sofosbuvir and simeprevir may be used only in patients ineligible or intolerant to peginterferon alfa (and urgent need of treatment [simeprevir]) the daclatasvir plus sofosbuvir and ledipasvir/sofosbuvir peginterferon-free regimens do not have such restrictions.[12-14] There are a number of adverse events associated with peginterferon (influenza-like symptoms, depression, and cytopenia) and ribavirin (haemolytic anaemia, fatigue, pruritus, and rash). The availability of the ledipasvir/sofosbuvir peginterferon-free regimen is expected to reduce the incidence and severity of adverse events, provide a simplified regimen, and a treatment option in patients who are ineligible for treatment with peginterferon or ribavirin.[3]

The pivotal phase III ION studies were conducted in treatment naïve and treatment experienced non-cirrhotic and cirrhotic patients with genotype 1 CHC. Ledipasvir/sofosbuvir treatment regimens achieved SVR12 rates of 93% to 99% which were significantly superior to the historical control rates. Furthermore the non-inferiority of treatment regimens in ION-3 was demonstrated, suggesting that the addition of ribavirin to the 8-week regimen of ledipasvir/sofosbuvir or extending the duration of treatment with ledipasvir/sofosbuvir to 12 weeks does not result in improved rates of SVR12 in treatment naive, non-cirrhotic patients. However the 12-week regimen is the standard regimen for patients without cirrhosis included in the SPC, with the 8-week regimen only being considered in previously untreated genotype 1-infected patients. Subgroup analyses indicated that treatment effect is maintained across a variety of patient subgroups, such as patients with cirrhosis and genotype 1a CHC. Efficacy data in patients with genotype 4 CHC is primarily limited to an on-going phase II study where SVR12 was achieved in 95% of patients.

Efficacy data for ledipasvir/sofosbuvir are limited to open-label studies, and the submitting company indicated that an indirect comparison was not possible as no comparator treatment arms were included. As such, comparative data (other than versus the historical controls in the pivotal studies)

are limited to a naive indirect comparison versus the comparator regimens considered of relevance by the submitting company: sofosbuvir + pegylated interferon + ribavirin for 12 weeks; simeprevir + pegylated interferon + ribavirin for 24 or 48 weeks; and simeprevir + sofosbuvir for 12 weeks.

The availability of ledipasvir/sofosbuvir will provide another peginterferon-free regimen. In patients with genotype 1 and 4 CHC, without cirrhosis or with compensated cirrhosis, the recommended treatment regimen is one tablet of ledipasvir/sofosbuvir daily for 12 to 24 weeks (8 weeks in non-cirrhotic patients who have previously untreated genotype 1 CHC). Clinical experts consulted by SMC considered that ledipasvir/sofosbuvir is a therapeutic advancement due to its simplified regimen and shorter duration of treatment compared to existing peginterferon-free regimens. Furthermore clinical experts considered that there may be service implications in terms of reduced monitoring, dose adjustment and supportive therapies for patients who would have previously received peginterferon-containing regimens.

Summary of comparative health economic evidence

The submitting company presented a lifetime cost-utility analysis comparing ledipasvir/sofosbuvir versus the following comparators in patients with genotypes (GT) 1 or 4 CHC:

- sofosbuvir+ pegylated interferon + ribavirin (PR) for 12 weeks
- simeprevir+PR for 24 or 48 weeks
- simeprevir+sofosbuvir for 12 weeks for patients who are ineligible/intolerant to interferon
- no treatment for patients who have previously failed a protease inhibitor+ pegylated interferon + ribavirin regimen.

The analysis was presented for treatment naive and treatment experienced groups separately and also an overall weighted average cost-effectiveness estimate based on an assumption about the relative mix of patient types in the population.

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 in the base case), 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 40-45 at the start of the model and 21% of patients were assumed to be cirrhotic at base line.

The key clinical data in the model related to the SVR rates and adverse events on treatment. These were taken from naive indirect comparisons of the relevant treatments. In the case of genotype 4 patients for ledipasvir/sofosbuvir, given a lack of data, the SVR data for genotype 1 rates were assumed to apply.

Utility values on treatment 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 0.75 or 0.55 for a patient with compensated cirrhosis. A key utility value was an assumed 0.04 increase in quality of life for patients experiencing an SVR, based on a published study. Similar assumptions have been used in other recent SMC submissions in terms of gains associated with an SVR. Given that quality of life data from the studies indicated good quality of life while on ledipasvir/sofosbuvir, the submitting company assumed there was no on-treatment decrement to quality of life associated with receiving ledipasvir/sofosbuvir whereas other treatments were associated with some reduction in quality of life.

Health state costs were largely taken from published sources and are similar to health state costs used in previous submissions to SMC. The analysis used a new source paper for the costs associated with liver transplants (not yet published) with these costs being higher than previous cost analyses.

The following results were estimated from the model:

	Ledipasvir/sofosbuvir versus	
	Sofosbuvir+PR	**Simeprevir +PR**
Genotype 1 treatment naive		
incremental costs	-£7,069	-£230
incremental quality adjusted life year (QALYs)	0.25	0.61
Incremental cost effectiveness ratio (ICER) (£/QALY)	Ledipasvir/sofosbuvir dominates (cheaper, more effective)	Ledipasvir/ sofosbuvir dominates
Genotype 4 treatment naive		
incremental costs	£1,066	£7,905
incremental QALYs	0.26	0.62
ICER	£4,088	£12,651
Genotype 1 and 4 treatment experienced		
incremental costs	£2,837	£5,498
incremental QALYs	0.48	0.56
ICER	£5,894	£9,788

The weighted average analysis indicated that ledipasvir/sofosbuvir would be the dominant treatment with a saving of £1,245 and a QALY gain of 0.40. For patients who were ineligible to receive an IFN regimen and for whom the company assumed sofosbuvir+simeprevir to be the appropriate comparator, the incremental cost-effectiveness ratio (ICER) was dominant for both treatment naïve and experienced patients. Ledipasvir/sofosbuvir resulted in savings of £27,057 and a QALY gain of 0.08 for treatment naïve patients with savings of £15,323 and a QALY gain of 0.01 for treatment experienced patients. For patients who had previously failed a protease inhibitor regimen and for whom no treatment was assumes as the only remaining option, the ICER was £14,415 on the basis of £31,766 in incremental costs and 2.2 QALYs gained.

A range of sensitivity analysis was presented and this indicated that the results were most sensitive to the overall on-treatment costs (comprised of drug acquisition, adverse event and monitoring costs) and to a lesser extent, the SVR for cirrhotic patients. For the GT1 treatment naive analysis, the results remained either dominant or under £10k per QALY against both comparators. For GT4 treatment naive patients the ICERs versus sofosbuvir+PR increased to £34-35k when the treatment costs for non- cirrhotic patients were varied by 25%, with figures of £22k-£25k when these parameters were varied in the comparison with simeprevir+PR. In the GT1 and GT4 treatment experienced analysis versus sofosbuvir+PR, the ICERs rose to £21k-£24k when treatment costs for non-cirrhotic patients were varied with estimates of £22k to £25k in the comparison with simeprevir+PR.

While the results show relatively low cost-effectiveness ratios, there were a number of issues with the analysis:

- The analysis assumed that regimens containing sofosbuvir and simeprevir are the standard therapies used in NHS Scotland and thus the treatments that would be displaced. SMC has only recently issued guidance on these medicines and expert responses confirmed that although there is some uptake other therapies are still used. The submitting company was therefore asked to re-run the analysis using other treatments as comparators. In response the company provided this analysis. The results are shown below for the relevant comparisons against pegylated interferon/ ribavarin or boceprevir/ telaprevir containing regimens. Additional sensitivity analysis was also provided around these ICERs which indicated that the results remained dominant in many cases and no ICER was above £22k.

Indication	**Comparator**		
	PR	**Telaprevir + PR**	**Boceprevir +PR**
GT1 treatment naïve	£7,985	Ledipasvir/sofosbuvir dominates	Ledipasvir/sofosbuvir dominates
GT4 treatment naïve	£12,715	-	-
GT1 and GT4 treatment experienced†	£12,491	£9,144	£3,551

- The analysis was driven by naive indirect comparisons. Clearly these are weaker forms of comparative evidence assessments upon which to base the economic model and this introduces uncertainty in to the results. However, it should be noted that the issue with indirect comparisons is similar to that seen in previous recent submissions for hepatitis C treatments. In addition, there is a lack of data in GT4 patients and thus the data for GT1 patients have been assumed to apply.
- The results were sensitive to the overall on-treatment costs, as shown above. As the treatment duration for ledipasvir is variable and the results are presented at an aggregate level, the results will have been influenced by the underlying assumptions about the composition of the population, for example, the % of cirrhotic patients or with other factors which may influence the duration of therapy according to the Summary of Product Characteristics (SPC). While the company varied the overall costs by +/-25% the submitting company was asked to provide additional analysis on specific aspects which influenced the overall medicine cost of ledipasvir/sofosbuvir. Changing the % of patients in the cohorts who were cirrhotic in the range 10% to 30% did produce some change in the ICERs but all scenarios remained under £18k per QALY. However, changes to the assumptions regarding the proportions of patients receiving 8, 12 or 24 weeks of treatment did have a more marked impact on the ICERs. The ICERs in GT1 treatment naive patients remained dominant or under £7.5k and under £15k in GT4 treatment naive patients but rose to £21k and £22k for GT1 and GT4 treatment experienced patients against sofosbuvir+PR and simeprevir+PR respectively when different assumptions were made. As such, the treatment durations used in practice could influence the cost-effectiveness of ledipasvir/sofosbuvir but the sensitivity analysis suggests that ledipasvir/sofosbuvir remains cost-effective in the sensitivity analysis provided. Given limited expert responses, it is difficult to get any information to validate the base case assumptions used regarding treatment durations.
- The analysis was presented at genotype level and did not present the results according to the patient's cirrhotic status, and cost-effectiveness may differ accordingly. Additional analysis was requested from the company and this showed that the ICERs were still under £25k for all groups, but in GT4 treatment naive and GT1 and 4 treatment experienced patients, the ICERs were lower in cirrhotic than non-cirrhotic patients.
- The analysis presented results comparing to sofosbuvir regimens in GT1 treatment experienced

patients. However, it should be noted that no clinical or economic data were presented for these patients in the SMC submission for sofosbuvir, which may imply greater uncertainty around the context for decision-making for this group.
- There were some concerns with the costs assumed for monitoring and the updated cost of transplants, but additional analysis provided by the company indicated that the results were not particularly sensitive to changes in these parameters.

While there are uncertainties associated with the indirect comparisons and some uncertainty associated with what treatments would be displaced, given the acceptable ICERs and robustness shown in sensitivity analysis against all comparators, the economic case has been demonstrated.

Summary of patient and public involvement

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

- Submissions were received from Hepatitis Scotland, The Hepatitis C Trust and Haemophilia Scotland, all registered charities.
- All three charities have received pharmaceutical company funding in the past two years with Hepatitis Scotland and The Hepatitis C Trust receiving some from the submitting company.
- Hepatitis C is a blood-borne virus which mainly infects the cells of the liver. This causes inflammation and damage to the liver as well as having other effects that can lead to the infected person being severely debilitated and prevent them from working. As a blood-borne virus it has a significant stigma associated with it which affects a person's social well-being and employability putting further strain on them and their carers.
- Current treatments can be lengthy and in the case of interferon can cause severe side effects both during and after treatment that patients find very difficult to cope with. These can cause them to come off treatment and prevent them achieving SVR.
- Ledipasvir-sofosbuvir is an interferon-free option that is taken orally as a tablet and has a shorter treatment duration with less side-effects than current therapies. This may help patients continue with their daily lives and may also make it easier for them to adhere to their treatment regime and achieve SVR.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guidance number 133; 'Management of hepatitis C' in 2006, which was updated in July 2013.[15] The guidelines include various recommendations for the management of CHC depending on a number of factors including genotype, previous treatment, co-infection with HIV. Peginterferon-free regimens are not included as the guideline predates their availability.

The British HIV Association published 'Guidelines for the management of hepatitis viruses in adults infected with HIV' in 2013.[16] The guidelines include various recommendations for the management of CHC depending on a number of factors including genotype, previous treatment and presence of cirrhosis. Peginterferon-free regimens are not included as the guideline predates their availability.

The European Association for Study of the Liver (EASL) published 'EASL Clinical Practice Guidelines: Management of hepatitis C virus infection', in 2014.[17] The guidelines include various recommendations for the management of CHC depending on a number of factors including genotype, previous treatment and presence of cirrhosis. Peginterferon-free regimens are not included as the guideline predates their availability.

EASL published 'EASL recommendations on treatment of hepatitis C', in April 2014.[18] The guidance provides advice on medicines approved by the European Medicines Agency up to the end of 2014, including sofosbuvir, simeprevir and daclatasvir. The guidelines will be updated as new medicines become available. Six treatment options including peginterferon-free regimens are detailed for genotype 1 and 4 CHC.

The World Health Organisation (WHO) published 'Guidelines for the screening, care and treatment of persons with hepatitis C infection', in April 2014.[19] The guidelines include various recommendations for the management of CHC including peginterferon-free regimens.

Additional information: comparators

Sofosbuvir, simeprevir, daclatasvir in peginterferon-free regimens or in combination with peginterferon plus ribavirin. Telaprevir and boceprevir in combination with peginterferon plus ribavirin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Peginterferon-free regimens		
ledipasvir/sofosbuvir	**90mg/400mg orally once daily for 8 to 24 weeks**	**24,987 to 77,960**
ledipasvir/sofosbuvir ribavirin	**90mg/400mg orally once daily for 24 weeks 1,000mg to 1,200mg orally daily for 24 weeks**	**79,567 to 79,810**
daclatasvir sofosbuvir	60mg orally daily for 12 to 24 weeks 400mg orally daily 12 to 24 weeks	59,502 to 119,004
daclatasvir sofosbuvir ribavirin	60mg orally daily for 24 weeks 400mg orally daily for 24 weeks 1,000mg to 1,200mg orally daily for 24 weeks	120,852
simeprevir sofosbuvir ± ribavirin	150mg orally daily for 12 weeks 400mg orally daily for 12 weeks 1,000mg to 1,200mg orally daily for 12 weeks	57,381 to 58,306
sofosbuvir ribavirin	400mg orally daily for 24 weeks 1,000mg to 1,200mg orally daily for 24 weeks	71,816
Peginterferon containing regimens		
daclatasvir peginterferon-alfa-2a ribavirin	60mg orally daily for 24 weeks 180 micrograms sc weekly 24 to 48 weeks 1,000mg to 1,200mg orally daily for 24 to 48 weeks	53,872 to 58,707
simeprevir peginterferon-alfa-2a ribavirin	150mg orally daily for 12 weeks 180 micrograms sc weekly for 24 to 48 weeks 1,000mg to 1,200mg orally daily for 24 to 48 weeks	27,234 to 32,069
sofosbuvir peginterferon-alfa-2a ribavirin	400mg orally daily for 12 to 24 weeks 180 micrograms sc weekly for 12 to 24 weeks 1,000mg to 1,200mg orally daily for 12 to 24 weeks	37,401 to 74,802

boceprevir peginterferon-alfa-2b ribavirin	800mg three times daily for 24 to 48 weeks 1.5 microgram/kg once weekly for 28 to 48 weeks 800mg to 1,800mg orally daily for 28 to 48 weeks	22,397 to 43,194
telaprevir peginterferon-alfa-2a ribavirin	2250mg daily in divided doses for 12 weeks 180 microgram sc once weekly for 24 to 48 weeks 1,000mg to 1,200mg orally daily for 24 to 48 weeks	27,234 to 32,069

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis (November 2014), MIMS and company's submission (ledipasvir/sofosbuvir). Costs are based on a body weight of 70kg (ribavirin dose of 1,000mg/day). sc=subcutaneously

Refer to SPCs for detailed information on regimens, duration of treatment and HCV genotype that treatments are used for.

Additional information: budget impact

The submitting company presented one composite budget impact estimate for genotypes 1 and 4 combined.

The submitting company estimated there to be 501 patients eligible for treatment with ledipasvir/sofosbuvir per year to which confidential estimates of treatment uptake were applied.

The submitting company estimated the gross medicines budget impact to be £7.4m in year 1 and £2.8m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £404k in year 1 and £151k in year 5. The displaced medicines cost related to a mix of sofosbuvir+ PR, simeprevir+PR and simpeprevir+sofosbuvir regimens; if these are not the displaced therapies then the extent of any cost savings may vary in practice. The calculations also assumed that 34% of patients would receive an 8 week treatment with ledipasvir/sofosbuvir, 61% a 12 week regimen and 6% a 24 week regimen.

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 09 January 2015.

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.