Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

ledipasvir/sofosbuvir 90mg/400mg film-coated tablet (Harvoni®)

SMC No. (1084/15)

Gilead Sciences Ltd

07 August 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 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 genotype 3 chronic hepatitis C (CHC) in adults.

SMC restriction: patients who are ineligible for or unable to tolerate interferon.

Efficacy data are limited to a phase II open-label study. The addition of ledipasvir to sofosbuvir plus ribavirin is expected to increase antiviral activity, although the magnitude of this effect is not well characterised.

SMC has previously accepted ledipasvir/sofosbuvir for restricted use in genotype 1 and 4 CHC; this now extends advice to include use in genotype 3 CHC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 07 September 2015

Indication

Treatment of chronic hepatitis C (CHC) in adults. (The current submission relates to genotype 3 CHC).

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 swallowed whole with or without food.

Genotype 3
Patients with cirrhosis and/or prior treatment failure: 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.

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 non-structural protein 5A (HCV NS5A) replication complex inhibitor, and sofosbuvir, a pan-genotypic inhibitor of the HCV NS5B RNA polymerase.[1] 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). In March 2015, SMC accepted ledipasvir/sofosbuvir for restricted use in genotype 1 and 4 CHC. The current submission for ledipasvir/sofosbuvir relates to use in genotype 3 CHC where it is administered with ribavirin. The submitting company has requested that SMC considers ledipasvir/sofosbuvir when positioned for use in patients who are ineligible for or unable to tolerate interferon.

Evidence in genotype 3 CHC comes from ELECTRON-2, an on-going phase II multicentre, open-label study, assessing the efficacy and safety of sofosbuvir-containing regimens for the treatment of chronic hepatitis C virus (HCV) infection. The study recruited patients aged ≥18 years, with chronic genotype 1, 2, 3, or 6 HCV infection and an HCV RNA ≥10,000 IU/mL at screening. Treatment experienced patients were required to have received ≥1 peginterferon- or standard interferon-containing regimen (which was not stopped due to an adverse event). Only treatment arms relevant to the current submission are discussed in this document. Treatment-naïve patients with genotype 3 CHC were randomised to ledipasvir/sofosbuvir 90mg/400mg once daily (n=25) or ledipasvir/sofosbuvir 90mg/400mg once daily + ribavirin (weight-based, <75kg; 1,000mg and ≥75kg; 1,200mg, given in divided doses) (n=26) for 12 weeks. In addition, 50 treatment-experienced patients with genotype 3 CHC received ledipasvir/sofosbuvir + ribavirin (doses as before) for 12 weeks. The primary endpoint was sustained virological response at 12 weeks post treatment (SVR12).[2-5]

In the treatment-naïve cohorts, SVR12 was achieved in 64% (16/25) of patients treated with ledipasvir/sofosbuvir and 100% (26/26) of patients treated with ledipasvir/sofosbuvir + ribavirin. In patients with cirrhosis, SVR12 was achieved in 33% (1/3) of patients treated with ledipasvir/sofosbuvir and 100% (5/5) of patients treated with ledipasvir/sofosbuvir + ribavirin. In patients without cirrhosis, SVR12 was achieved in 68% (15/22) of patients treated with ledipasvir/sofosbuvir and 100% (21/21) of

patients treated with ledipasvir/sofosbuvir + ribavirin. In the ledipasvir/sofosbuvir group, eight patients relapsed and one patient withdrew due to adverse events.[3,6,7]

In the treatment-experienced cohort, SVR12 was achieved in 82% (41/50) of patients treated with ledipasvir/sofosbuvir + ribavirin: 73% (16/22) of patients with cirrhosis and 89% (25/28) of patients without cirrhosis. There was one patient (2.0%) with virological breakthrough at week 12 (a patient without cirrhosis) and eight patients (16%) relapsed.[4]

Additional efficacy data, collected by HCV Research UK, are available for patients with decompensated cirrhosis (genotype 1 or 3 CHC) treated with ledipasvir/sofosbuvir ± ribavirin (or daclatasvir + sofosbuvir ± ribavirin) via an early access scheme in NHS England. SVR12 was achieved in 59% of patients with genotype 3 CHC treated with ledipasvir/sofosbuvir + ribavirin.[8]

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

Summary of evidence on comparative safety

In treatment-naïve patients, 100% (25/25) in the ledipasvir/sofosbuvir group and 88% (23/26) in the ledipasvir/sofosbuvir + ribavirin group reported an adverse event. Serious adverse events occurred in four patients (16%) and grade 3/4 adverse events in three patients (12%); all were treated with ledipasvir/sofosbuvir. Adverse events occurring in the ledipasvir/sofosbuvir and ledipasvir/sofosbuvir + ribavirin groups respectively included: headache (40% versus 31%), upper respiratory tract infection (36% versus 35%), nausea (36% versus 15%), fatigue (20% versus 7.7%), insomnia (12% versus 12%), cough (12% versus none), haemolytic anaemia (none versus 15%) and rash (4.0% versus 3.8%). Grade 3/4 laboratory abnormalities occurred in 4.0% of patients in the ledipasvir/sofosbuvir group and 27% of patients in the ledipasvir/sofosbuvir + ribavirin group. No patients in the ledipasvir/sofosbuvir group had haemoglobin <10g/dL, compared with 12% of patients in the ledipasvir/sofosbuvir + ribavirin group. No patients had haemoglobin <8.5g/dL.[3]

In treatment-experienced patients, 90% (45/50) reported an adverse event and 2.0% (1/50) of patients each reported a grade 3/4 adverse event and serious adverse event. Adverse events reported included: fatigue (26%), headache (26%), insomnia (20%), upper respiratory tract infection (18%), rash (14%), nausea (10%), diarrhoea (8.0%), irritability (8.0%), lethargy (6.0%) and pruritis 6.0%. Grade 3/4 laboratory abnormalities occurred in 16% of patients and haemoglobin <10g/dL in 4.0% of patients. No patients had haemoglobin <8.5g/dL.[4]

Summary of clinical effectiveness issues

The treatment of CHC is changing rapidly with the availability of peginterferon-free treatment regimens which have improved efficacy and adverse event profiles compared to peginterferon-containing regimens.[6] The submitting company has requested that SMC considers ledipasvir/sofosbuvir plus ribavirin when positioned for use in patients who are ineligible for or unable to tolerate interferon. For genotype 3 CHC, ledipasvir/sofosbuvir plus ribavirin is licensed for use in patients with cirrhosis and/or prior treatment failure 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.[9]

There are limited peginterferon-free treatment options for genotype 3 CHC in Scotland; the sofosbuvir plus ribavirin regimen was restricted by SMC to patients ineligible for, or who are unable to tolerate peginterferon alfa, and the daclatasvir plus sofosbuvir plus ribavirin regimen to patients with significant

fibrosis (Metavir scores F3-F4) or compensated cirrhosis. Clinical experts consulted by SMC considered there was unmet need in terms of availability of treatments for genotype 3 CHC.

In the ELECTRON-2 study, SVR12 was achieved in 100% of treatment-naïve patients and 82% of treatment-experienced patients who received ledipasvir/sofosbuvir plus ribavirin for 12 weeks.[3,4] SVR12 has been used in recent CHC studies as the primary outcome, and has been accepted by European and US regulatory bodies in view of the high concordance (98% to 99%) between SVR12 and SVR24.[7]

There are some limitations with the study in terms of patient population and treatment duration. Treatment experienced patients were required to have received ≥1 peginterferon- or standard interferon-containing regimen (which was not stopped due to an adverse event). It is not clear whether patients recruited to the study were specifically ineligible for (contraindicated) or intolerant of interferon (discontinued interferon treatment due to intolerance). Efficacy for treatment-naïve patients with cirrhosis is limited to data from five patients. The treatment duration in the study (12 weeks) is shorter than recommended in the SPC (24 weeks). The European Medicines Agency (EMA) commented that preliminary data for treatment-experienced patients in the ELECTRON-2 study (available at the time of regulatory approval) and, in particular the number of relapses, suggested that 12 weeks duration is not the optimised treatment duration. However, the EMA considered that the data indicated that ledipasvir in addition to sofosbuvir plus ribavirin increases the likelihood of an SVR in patients in whom sofosbuvir plus ribavirin is not an optimal treatment regimen. Therefore ledipasvir/sofosbuvir plus ribavirin was licensed for use in patients with cirrhosis and/or prior treatment failure for a treatment duration of 24 weeks. As the marketing authorisation is based on an assumption of efficacy, there is no accurate estimate of the magnitude of treatment effect for the addition of ledipasvir to the sofosbuvir plus ribavirin regimen in the licensed population.[7]

The treatment regimen for ledipasvir/sofosbuvir is similar to comparator peginterferon-free treatment regimens which are also licensed for a 24 week duration: sofosbuvir + ribavirin or daclatasvir + sofosbuvir + ribavirin.[10,11] However, clinical experts consulted by SMC have indicated that 12 week duration is used for daclatasvir + sofosbuvir + ribavirin and is likely to be used for ledipasvir/sofosbuvir + ribavirin. They considered that the place in therapy of ledipasvir/sofosbuvir + ribavirin is in place of daclatasvir + sofosbuvir + ribavirin.

There are no head-to-head studies versus relevant comparator regimens, and lack of control arms in the studies meant that the submitting company was unable to conduct an adjusted indirect comparison or network meta-analysis. Consequently, efficacy data for the economic analysis are limited to a naïve comparison of SVR12 rates with comparators. However, due to lack of available data a proxy population (treated with daclatasvir + sofosbuvir for 12 weeks) was used for the daclatasvir + sofosbuvir + ribavirin comparator regimen. Other recent submissions to SMC for CHC have also had issues with lack of comparative data/robust indirect comparison.

A risk of bradycardia and heart block is likely to be related to co-prescribing of ledipasvir/sofosbuvir (or daclatasvir + sofosbuvir) with amiodarone, although the mechanism of action is unknown. The EMA commented that amiodarone should only be used with ledipasvir/sofosbuvir or daclatasvir + sofosbuvir when no other anti-arrhythmics can be prescribed.[12]

Summary of comparative health economic evidence

The submitting company presented a lifetime cost-utility analysis comparing a 24 week regimen of ledipasvir/sofosbuvir+ ribavirin (LDV/SOF/RBV) versus the following comparators in interferon-ineligible genotype 3 patients who were treatment-naïve with cirrhosis or treatment-experienced patients with or without cirrhosis:

- sofosbuvir + ribavirin (SOF/RBV) for 24 weeks
- daclatasvir+sofosbuvir+ribavirin (DCV/SOF/RBV) for 24 weeks

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 general population mortality rates were also applied to each state of the model. Advanced liver disease states were also associated with excess mortality. 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 (treatment-naïve) or 45 (treatment-experienced) at the start of the model.

The key clinical data in the model related to the SVR rates and adverse events on treatment. These were taken from key clinical trials of the relevant regimens through a naïve comparison.

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. A 5% utility decrement was also applied when on each treatment regimen.

Health state costs were largely taken from published sources and are similar to health state costs used in previous submissions to SMC.

The following results in terms of costs and quality adjusted life years (QALYs) were estimated from the model for each treatment option:

Genotype 3 treatment naïve IFN-ineligible patients with compensated cirrhosis

Technologies	QALYs	Costs
DCV+SOF+RBV	8.05	£152,114
SOF+RBV	9.68	£95,686
LDV/SOF+RBV	10.02	£102,375

The results indicated that for treatment-naïve cirrhotic patients, LDV/SOF/RBV is cost-effective against both comparators as it is dominates DCV/SOF/ RBV and has an incremental cost-effectiveness ratio (ICER) of £19,751 compared to SOF/RBV on the basis of an incremental cost of £6,689 and a quality adjusted life year (QALY) gain of 0.34.

Genotype 3 treatment experienced IFN-ineligible patients – non-cirrhotic and cirrhotic cohorts

Non-cirrhotic			Cirrhotic		
Technologies	**QALYs**	**Costs**	**Technologies**	**QALYs**	**Costs**
SOF+RBV	15.41	£76,358	SOF+RBV	7.93	£100,432
LDV/SOF+RBV	15.48	£84,235	DCV+SOF+RBV	8.26	£147,987
DCV+SOF+RBV	15.57	£124,599	LDV/SOF+RBV	8.37	£106,415

In treatment-experienced patients who are non-cirrhotic, the incremental cost-effectiveness ratio (ICER) versus DCV/SOF/RBV was in the south-west quadrant of the cost-effectiveness plane i.e. LDV/SOF/RBV is both cheaper and less effective (£40,364 less and 0.1 less QALYS) than the comparator regimen such that the ICER for DCV/SOF/RBV (as the more effective treatment) over LDV/SOF/RBV is over £407k. Compared to SOF/RBV, LDV/SOF/RBV would not be considered cost-effective as the ICER is £128k on the basis of small additional QALYs and an additional cost of £8k. The submitting company emphasised that these results were on the basis of 12 week data for LDV/SOF/RBV and thus may underestimate the effectiveness of the 24 week regimen.

For treatment-experienced cirrhotic patients, the results indicated that LDV/SOF/RBV would be considered cost-effective against both comparators, being dominant over DCV/SOF/RBV and an ICER of £13,593 over SOF/RBV on the basis of an incremental cost of £5,983 and a QALY gain of 0.44.

One-way sensitivity analysis showed that the results were most sensitive to changing the overall cost of treatments or from changing the SVR. In most cases, the ICER remained within cost-effective limits but if low SVRs were assumed for LDV/SOF/RBV (or conversely, high SVR rates for the comparator regimens), LDV/SOF/ RBV became a dominated regimen in some cases. For example, in treatment-naïve cirrhotic patients compared to SOF/RBV. if the SVR for the comparator was increased to 99.8% or the SVR for LDV/SOF/ RBV decreased to 86.8%, the treatment became dominated.

Scenario analysis was also provided to show the impact of assuming that the LDV and DCV regimens would be used for a 12 week treatment duration. This resulted in LDV being cost-effective in all scenarios. It was the dominant therapy in treatment-experienced cirrhotic patients and treatment-naïve cirrhotic patients. It would was also dominant over SOF/RBV (24 weeks) in treatment-experienced non-cirrhotic patients; compared to DCV/SOF/RBV (12 weeks) in this same patient group, it would be associated with less QALYs and is cost-saving but the ICER for the DCV regimen would not be considered cost-effective at £187k per QALY over LDV/SOF/RBV.

There were a number of weaknesses associated with the analysis:

- The analysis was driven by naïve comparisons. These are weaker forms of comparative evidence assessments upon which to base the economic model and this introduces uncertainty into the results. However, it should be noted that the issue with naive comparisons is similar to that seen in previous recent submissions for hepatitis C treatments.
- There were further weaknesses in the comparative evidence base, for example, because the SVRs for the DCV arm were assumed from data on 12 weeks of treatment with DCV/SOF from the ALLY-3 study rather than from 24 weeks of treatment with DCV/SOF/RBV. It may be that the absence of RBV from the regimen and the use of a 12 week rather than 24 week duration could have resulted in lower responses being used for the comparator regimen in the model. However, the sensitivity analysis indicated that the results were relatively stable to assuming different SVRs for DCV/SOF/RBV.

- The cost-effectiveness results for the treatment-experienced non-cirrhotic patient group showed variability in terms of the ICERs against the alternative treatment options, being judged cost-effective against DCV/SOF/RBV on the basis of an ICER in the south-west quadrant but not cost-effective against SOF/RBV. The New Drugs Committee noted that the ICERs may show some volatility as a result of small differences between treatments. In addition, the analysis which showed that LDV/SOF/RBV would be judged cost-effective against both treatment options if a 12 week treatment duration was assumed for the LDV and DCV regimens was helpful given that SMC experts had indicated that this may be how the regimen would be used in practice.
- The SVR rates for LDV/SOF/RBV were based on data from 12 weeks of use but the economic analysis modeled the cost of a 24 week treatment duration, as per the SPC.

While there are uncertainties associated with the naive comparisons and some uncertainty associated with what treatments would be displaced, given the acceptable ICERs and robustness shown in sensitivity analysis for most patients and against the comparator regimens, 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 the Hepatitis C trust and Haemophilia Scotland. The Hepatitis C Trust is a registered charity and Haemophilia Scotland is a Scottish Charitable Incorporated Organisation (SCIO).

- The Hepatitis C trust has received pharmaceutical company funding in the past two years, including from the submitting company Haemophilia Scotland is a recently formed SCIO and has not received any pharmaceutical company funding thus far. The previous organisation had received pharmaceutical company funding in the past two years but not from the submitting company.

- Hepatitis C is a blood-borne virus that predominantly infects the cells of the liver. It can affect the liver's ability to perform its essential functions. People living with the disease can be seriously debilitated and may not be able to work. It is a significantly stigmatized disease and there have been people who have lost their jobs on revealing their HCV status.

- Some patients are intolerant of pegylated interferon and some have been unwilling to access treatment because of side effects and lengthy treatment durations. Ledipasvir/sofosbuvir provides an effective interferon-free treatment with a reduced treatment duration.

- Ledipasvir/sofosbuvir will provide a regimen that is likely to help more patients achieve SVR as it is a single pill daily oral tablet. Patients with bleeding disorders and genotype 3 HCV who have typically been infected for over 30 years have often been unsuccessful in achieving SVR with current standard treatments. Ledipasvir/sofosbuvir would provide them with a new treatment option.

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.[13] Recommendations in relation to the management of CHC include:

- All patients with chronic HCV infection should be considered for antiviral therapy.
- Sustained viral response should be used as a marker for viral clearance.
- For patients with HCV 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 virological response (RVR) at week 4 of therapy, could be considered for shortened duration of therapy of 12 to 16 weeks.
- In treatment-experienced patients with a lower likelihood of SVR, benefits of treatment need to be weighed against potential risks and side effects.
- Response-guided therapy can only be used in treatment-naïve patients and previous treatment relapsers who are not cirrhotic.
- Patients co-infected with hepatitis B and C should be considered for treatment with pegylated interferon and weight-based ribavirin.
- Co-infected genotype 2 or 3 patients who achieve an RVR may be considered for 24 weeks of treatment.

The National Institute for Health and Care Excellence (NICE) published Multiple Technology Appraisal Guidance number 200, 'Use of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C' in 2010.[14] It recommends peginterferon alfa (2a or 2b) plus ribavirin as a possible treatment for people with CHC:

- who have been treated previously with peginterferon alfa (2a or 2b) plus ribavirin, or with peginterferon alfa monotherapy, but their hepatitis C didn't improve, or improved but then got worse again.
- or who also have an HIV infection.
- NICE recommends short courses of treatment with peginterferon alfa (2a or 2b) plus ribavirin for people whose hepatitis C has greatly improved within 4 weeks of starting treatment and who are suitable for short treatment courses.

The British HIV Association published 'Guidelines for the management of hepatitis viruses in adults infected with HIV', in 2013.[15] Recommendations include:

- all patients should be managed by a clinician experienced in the management of both HIV and hepatitis C or should be jointly managed by clinicians from HIV and hepatitis backgrounds.
- all patients with HCV/HIV infection should be assessed for suitability for treatment of hepatitis C.

For those with genotype 3, treatment recommendations include:

- standard treatment with pegylated interferon and ribavirin for 48 weeks unless RVR is achieved, when treatment should be shortened to 24 weeks if the patient is non-cirrhotic.

The European Association for Study of the Liver (EASL) published 'EASL Clinical Practice Guidelines: Management of hepatitis C virus infection', in 2014.[16] The guidelines includes the following recommendations for genotype 2, 3, 4, 5 and 6 treatment naïve patients:

- The combination of peginterferon-α and ribavirin is the approved standard of care for chronic hepatitis C genotype 2, 3, 4 ,5, and 6
- Ribavirin should be given at a weight-based dose of 15mg/kg for genotypes 4, 5, and 6 and at a flat dose of 800mg/day for genotypes 2 and 3
- Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at the dose of 15mg/kg.

EASL updated 'EASL recommendations on treatment of hepatitis C', in 2015.[17] The guidance provides advice on medicines approved by the European Medicines Agency. For genotype 3 CHC, three treatment options are detailed (see guidance for specific details) for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on peginterferon-a and ribavirin:

option 1: peginterferon + ribavirin + sofosbuvir
option 2: sofosbuvir + ribavirin
option 3 sofosbuvir + daclatasvir.

The World Health Organisation (WHO) published 'Guidelines for the screening, care and treatment of persons with hepatitis C infection', in April 2014.[18]
The guidelines include the following recommendations for treatment:

- Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin.
- Sofosbuvir, given in combination with ribavirin with or without pegylated interferon (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than pegylated interferon and ribavirin alone (or no treatment for persons who cannot tolerate interferon).

The following recommendations were proposed for genotype 3 patients by the British Association for the Study of the Liver at a consensus meeting on Therapy for Chronic Hepatitis C in London on 3 March 2015.[19]

- In patients with no evidence of cirrhosis/severe fibrosis:
    - peginterferon/ribavirin for 24 weeks (12 to 16 weeks in low viral load/rapid viral response) is recommended in treatment naïve patients.
    - sofosbuvir + daclatasvir ± ribavirin or ledipasvir/sofosbuvir ± ribavirin for 12 weeks is recommended for those intolerant of interferon.
    - preferred therapy is sofosbuvir + peginterferon + ribavirin for 12 weeks for patients who are treatment-experienced.

- In patients with compensated cirrhosis/severe fibrosis/major extra-hepatic manifestations, the preferred treatment is sofosbuvir + peginterferon + ribavirin for 12 weeks. For those intolerant of interferon the following treatment options are all acceptable: sofosbuvir + daclatasvir + ribavirin for 12 weeks; ledipasvir/sofosbuvir + ribavirin for 12 weeks; sofosbuvir + ribavirin for 24 weeks.

- In patients with decompensated cirrhosis treatment is recommended with either: ledipasvir/sofosbuvir ± ribavirin for 12 weeks; sofosbuvir + daclatasvir ± ribavirin for 12 weeks.

[NB some treatment durations are out with the marketing authorisations of the medicines]

Additional information: comparators

Daclatasvir + sofosbuvir + ribavirin (for 24 weeks); sofosbuvir + ribavirin (for 24 weeks).

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
ledipasvir/sofosbuvir ribavirin	**90mg/400mg orally once daily for 24 weeks 1,000mg to 1,200mg orally daily for 24 weeks**	**79,810**
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
sofosbuvir ribavirin	400mg orally daily for 24 weeks 1,000mg to 1,200mg orally daily for 24 weeks	71,816

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis and MIMs on 27 May 2015. Costs are based on a body weight of 70kg (ribavirin dose of 1,000mg/day).

Additional information: budget impact

The submitting company estimated there to be 33 patients eligible for treatment with LDV/SOF/RBV to which a confidential estimate of patient uptake was applied. The figures were arrived at assuming that only 2.7% of hepatitis C patients are treated.

The submitting company estimated the gross medicines budget impact to be £1.3m in year 1 and £261k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £428k in year 1 and £86k in year 5. The displaced medicines cost related to 70% displacement of the DCV/SOF/RBV and 30% displacement of SOF/RBV. All patients were assumed to receive a 24 week regimen.

*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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4. Gane EJ, Hyland RH, An D, et al. High Efficacy of LDV/SOF Regimens for 12 weeks for patients with HCV genotype 3 or 6 Infection. Poster LB-11 Presented at AASLD, 7-11 November 2014 Boston, MA 2014.

5. *Commercial in Confidence**

6. *Commercial in Confidence**

7. European Medicines Agency. European Public Assessment Report for Harvoni (ledipasvir/sofosbuvir). 25 September 2014. EMA/702742/2014.

8. Foster G, McLauchlan J, Irving W, et al. Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV Genoypes 1 and 3. Oral presentation presented at 50th annual meeting of the European Association for the Study of the Liver 22-26 April 2015, Vienna, Austria 2015.

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11. Bristol Myers Squibb. Summary of product characteristics for daclatasvir (Daklinza®). Last updated 17 September 2014.

12. European Medicines Agency. Press release; EMA recommends avoidance of certain hepatitis C medicines and amiodarone together. 24 April 2014. EMA/258577/2015

13. Scottish Intercollegiate Guidelines Network (SIGN). Guideline number 133, management of hepatitis C, July 2013

14. National Institute for Health and Care Excellence. Multiple technology appraisal number 200. Use of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C. 2010.

15. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. HIV Medicine (2013), 14 (Suppl. 4), 1-71

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18. WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection, April 2014.
http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1

19. Consensus Meeting on Therapy for Chronic Hepatitis C. 3 March 2015. Available at http://www.basl.org.uk/news/146/Final-Recommendations-for-new-HCV-drugs/index.cfm

This assessment is based on data submitted by the applicant company up to and including 17 July 2015.

**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.