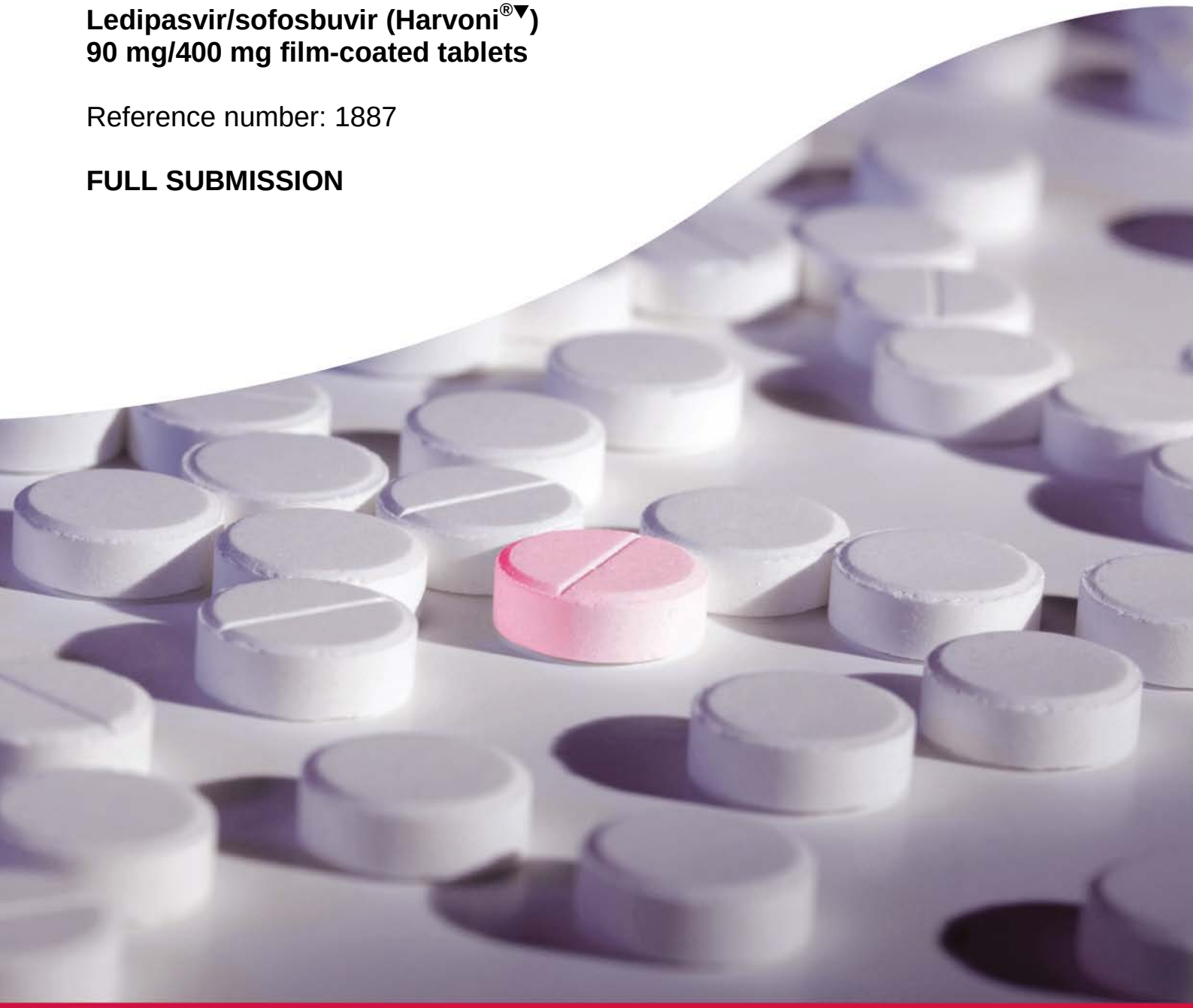
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Ledipasvir/sofosbuvir (Harvoni®▼)
90 mg/400 mg film-coated tablets

Reference number: 1887

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Ledipasvir/sofosbuvir (Harvoni®▼) 90 mg/400 mg film-coated tablets

This assessment report is based on evidence submitted by Gilead Sciences Limited on 10 December 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Ledipasvir/sofosbuvir (Harvoni®▼) for the treatment of chronic hepatitis C in adults. For hepatitis C virus genotype-specific activity see Summary of Product Characteristics (SPC)[2]
Dosing	The recommended dose is one tablet once daily with or without food. For patients with genotypes 1 or 4 without cirrhosis the recommended duration of treatment is 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. For patients with genotypes 1 or 4 with compensated cirrhosis the recommended duration of treatment is 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 genotypes 1 or 4 with decompensated cirrhosis or who are pre-/post-liver transplant should be treated with ledipasvir/sofosbuvir and ribavirin for 24 weeks. Patients with genotype 3, with cirrhosis and/or prior treatment failure should be treated with ledipasvir/sofosbuvir and ribavirin for 24 weeks. Refer to SPC for further information regarding dosing details[2].
Marketing authorisation date	17 November 2014[2].

2.0 DECISION CONTEXT

2.1 Background

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide[3]. Approximately one in five patients infected with HCV will clear it naturally from their body within the first six months of infection[4]. For the remaining patients, HCV is a chronic infection that can span several decades, be life-long and can cause liver cirrhosis, liver cancer and lead to the need for liver transplantation[4]. The estimated number of people in Wales with chronic HCV infection is 12,000 (0.4% of the population)[5].

Six main HCV genotypes, and a large number of subtypes have been described with genotypes 1 and 3 each accounting for about 40-50% of infected patients in Wales[3,6]. The primary goal of HCV therapy is to cure the infection, which is generally associated with resolution of liver disease in patients without cirrhosis[3]. In patients with cirrhosis, HCV eradication reduces the rate of decompensation and the risk of hepatocellular

carcinoma[3]. The infection is cured in more than 99% of patients who achieve a sustained virological response (SVR), defined as undetectable HCV RNA 12 or 24 weeks after treatment completion[3,7].

The National Institute for Health and Care Excellence (NICE) recommends antiviral therapy (AVT) with a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) for patients infected with all HCV genotypes with the addition of a protease inhibitor as triple therapy in patients with HCV genotype 1[6,8,9]. However interferon has limited efficacy in many patients and is associated with serious side effects including risk of hepatic decompensation and septicaemia in patients with advanced liver disease, as well as bone marrow suppression and psychiatric side effects such as depression[7].

Single agent sofosbuvir (SOF), a pan-genotypic, nonstructural protein 5B (NS5B) RNA polymerase inhibitor, is licensed for use in combination with other medicinal products for the treatment of chronic hepatitis C[10]. Ledipasvir (LDV) which is only available in combination with sofosbuvir (as Harvoni®▼) is a new NS5A protein inhibitor, which is essential for RNA replication and the assembly of HCV virions[2]. The submitting company have included economic analyses for HCV genotypes 1 and 4 but not genotype 3[1]. Ledipasvir/sofosbuvir (LDV/SOF) has not been studied against genotypes 2, 5 and 6 and therefore in the summary of product characteristics there is a recommendation that this treatment should not be used in patients infected with these genotypes[2].

2.2 Comparators

The comparators included in the company submission were:

- SOF and PEG-IFN and RBV
- Simeprevir (SMV) and PEG-IFN and RBV
- SMV and SOF
- telaprevir (TPV) and PEG-IFN and RBV
- boceprevir (BOC) and PEG-IFN and RBV
- PEG-IFN and RBV
- No treatment.

See section 4.1.1.

2.3 Guidance and related advice

- European Association for the Study of the Liver clinical practice guidelines: management of hepatitis C virus infection (2014)[3].
- World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection (2014)[11].
- SIGN guidance 133. Management of hepatitis C (2013)[12].
- NICE. Technology Appraisal (TA) 252. Telaprevir for the treatment of genotype 1 chronic hepatitis C (2012)[9].
- NICE. TA 253. Boceprevir for the treatment of genotype 1 chronic hepatitis C (2012)[8]
- NICE. Technology appraisal 200: Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (2010)[6].

The All Wales Medicines Strategy Group (AWMSG) has previously issued a recommendation for the use of eltrombopag (Revolade®▼)[13]. Daclatasvir (Daklinza®▼) is currently being appraised by AWMSG[14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes three phase III studies (ION 1–3) and seven phase II studies (five of which are ongoing):SOLAR 1, ELECTRON 2, SYNERGY, ERADICATE, SIRIUS, ELECTRON and LONESTAR examining the efficacy of LDV/SOF with and without RBV in patients with HCV[1]. Two phase III studies, ION1 and ION3 considered exclusively treatment-naive patients and these are discussed together in section 3.1. ION2, a phase III study of treatment experienced patients, is discussed in section 3.2. Phase II studies of LDV/SOF discussed in section 3 are: SOLAR1 a study of patients either post liver transplant or with advanced liver disease, ELECTRON 2 which included patients with HCV genotype 3, SYNERGY which includes patients with HCV genotype 4; ERADICATE, a study of patients co-infected with HCV and HIV, and SIRIUS which provides safety data for LDV/SOF treated patients versus those treated with placebo. The LONESTAR and ELECTRON studies are phase II studies conducted in patients with HCV genotype 1 and provide little additional data compared to the ION studies and therefore are not discussed further in this report[1].

3.1 ION 1 and ION 3 studies.

ION1 and ION3 were open-label, multicentre studies designed to investigate the efficacy of LDV/SOF therapy in patients with chronic genotype 1 HCV infection, having no previous exposure to either PEG-IFN or RBV[1,7,15,16]. The studies did not include either active comparator or placebo arms. In ION1 patients (n=865) were randomised to four different treatment arms: LDV/SOF for 12 weeks, LDV/SOF and RBV for 12 weeks, LDV/SOF for 24 weeks or LDV/SOF and RBV for 24 weeks. In ION3 patients (n=647) were randomised to three different treatment arms: LDV/SOF for 8 weeks, LDV/SOF and RBV for 8 weeks or LDV/SOF for 12 weeks. The number of patients in ION 1 with compensated cirrhosis was 136 (16%) and 11 patients (1.3%) had HCV genotypes other than type 1. All patients in the ION 3 study were HCV genotype 1 with the absence of cirrhosis.

The primary endpoint was the sustained virologic response measured 12 weeks post-treatment (SVR12) and defined as the proportion of patients having HCV RNA less than the lowest limit of quantitation (25 IU/ml) at 12 weeks following the end of treatment. Results for the primary endpoint are shown in Table 1. SVR12 values of between 93–100% were obtained for the different arms of the studies. In treatment naive patients with compensated cirrhosis, 12 weeks of LDV/SOF yielded high SVR rates and the addition of RBV did not confer any apparent increase in efficacy. In the ION3 study relapse rates were higher for patients who received 8 weeks of treatment versus those receiving 12 weeks of treatment. A high proportion of patients who relapsed (9 of 11 patients) and who received 8 weeks of LDV/SOF had baseline HCV RNA ≥ 6 million IU/ml[1,7,15,16].

Table 1: Results for ION1 and ION3 studies[1,7,15,16].

	ION 1				ION 3		
	LDV/SOF (n = 214)	LDV/SOF +RBV (n = 217)	LDV/SOF (n = 217)	LDV/SOF + RBV (n = 217)	LDV/SOF (n = 215)	LDV/SOF+ RBV (n = 216)	LDV/SOF (n = 216)
Weeks of treatment	12	12	24	24	8	8	12
SVR12 in all patients	211 (99%)	211 (97%)	213 (98%)	215 (99%)	202 (94%)	201 (93%)	208(96%)
SVR12 in cirrhotic patients	32/34 (94%)	33/33 (100%)	32/33 (97%)	36/36 (100%)	-	-	-
Number of patients relapsing*	1 (0.5%)	0	1 (0.5%)	0	11 (5%)	9 (4%)	3(1%)

LDV: ledipasvir; SOF: sofosbuvir; RBV: ribavirin; SVR12: sustained virologic response measured 12 weeks post-treatment.
*other causes of patient's non-response included patients lost to follow-up or those withdrawing consent.

Health-related quality of life (HRQL) measurements were unchanged between baseline and end of treatment for the LDV/SOF treated patients but were reduced in those treated with LDV/SOF and ribavirin[1].

3.2 ION 2 study.

In ION2 the efficacy of LDV/SOF therapy in patients with chronic genotype 1 HCV infection, having not had a SVR after treatment with PEG-IFN and RBV (with or without boceprevir or telaprevir) was studied[1,7,17]. The study was open-label and multicentred but did not include either active comparator or placebo arms. Patients (n=440) were randomised to four different treatment arms: LDV/SOF for 12 weeks, LDV/SOF and RBV for 12 weeks, LDV/SOF for 24 weeks or LDV/SOFand RBV for 24 weeks.

Results for the primary endpoint, SVR12, are shown in Table 2. High SVR12 rates of between 94–99% were obtained for the different arms of the study both with and without RBV, with relapses being more frequent in the 12 week arms. Subgroup analysis suggested a difference (p = 0.007) in SVR response for cirrhotic patients after 12 weeks of treatment versus after 24 weeks of treatment but this observation is preliminary, since the study was not powered for intergroup comparisons. The additional use of RBV did not improve the SVR response (see Table 2). Patients treated with LDV/SOF and RBV had statistically significant worsening in HRQL questionnaire scores between baseline and end of treatment, whilst patients treated with LDV/SOF alone had no decrements in HRQL scores[1,7,17].

Table 2: Results for ION2 study[1,7,17].

	LDV/SOF (n = 109)	LDV/SOF+RBV (n = 111)	LDV/SOF (n = 109)	LDV/SOF +RBV (n = 111)
Weeks of treatment	12	12	24	24
SVR12 (all patients)	102 (94%)	107 (96%)	108* (99%)	110† (99%)
SVR12 in cirrhotic patients	19/22 (86%)	18/22 (82%)	22/22 (100%)	22/22 (100%)
SVR12 in non cirrhotic patients	83/87 (95%)	89/89 (100%)	86/87 (99%)	88/89 (99%)
Number of patients relapsing (all patients)	7 (6%)	4 (4%)	0	0

LDV: ledipasvir; SOF: sofosbuvir; RBV: ribavirin; SVR12: sustained virologic response measured 12 weeks post-treatment; CI: confidence interval.
*one patient withdrew consent after the post-treatment week 4 visit; at this visit, the HCV RNA level was less than 25 IU/ml.
†one patient did not adhere to the study treatment and had a virological breakthrough during treatment.

3.3 SOLAR 1 study.

The ongoing phase II SOLAR 1 study enrolled patients with HCV infection (and predominately chronic genotype 1) either with advanced liver disease (pre liver transplant) or post liver transplant[1]. SOLAR 1 is an open-label, multicentred study with patients randomised to either 12 or 24 weeks of treatment with LDV/SOF plus RBV. Considering the 24 week treatment arm only, as this is consistent with the licensed indication, 42 of 47 (89%) pre-transplant patients with decompensated cirrhosis achieved SVR12. In those patients who were post transplant without decompensated cirrhosis, 55 out of 56 (98%) achieved SVR12. For decompensated patients post transplant, SVR12 was achieved for 15 of 18 (83%) patients with Child Pugh Turcotte (CPT, see Glossary) class B cirrhosis [commercial in confidence data removed][1].

3.4 ELECTRON 2 study.

The ongoing phase II ELECTRON 2 study included 51 treatment naive patients with HCV genotype 3 with compensated cirrhosis or without cirrhosis[1,7]. Following 12 weeks of treatment SVR12 was achieved for all 26 patients (100%) in the LDV/SOF plus RBV arm and for 16 of 25 patients (64%) in the LDV/SOF arm[1,7].

3.5 SYNERGY study.

The ongoing phase II SYNERGY study (CO-US-337-0117) includes treatment naive and experienced patients with and without compensated cirrhosis with HCV genotype 4. SVR12 was achieved by 19 of 20 patients (95%) following 12 weeks of treatment with LDV/SOF. One additional patient has achieved SVR8 to date with SVR12 data awaited. [1,7].

3.6 Comparative safety.

Pooled results from the ION phase III studies showed that the frequency of serious adverse events (SAEs) was low[7]. Treatment-related SAEs occurred for four in 1080 patients (0.4%) in the LDV/SOF arms and for one in 872 patients (0.1%) in the LDV/SOF plus RBV arms[7]. In total six treatment–related SAEs were reported in five patients including two occasions of anaemia in a patient treated with LDV/SOF and RBV, which resolved after RBV dose reduction. Four SAEs were reported for patients receiving LDV/SOF: acute mesenteric vein thrombosis in a patient with numerous comorbidities, factor VIII inhibition in a patient with known mild haemophilia, salpingitis which resolved without interrupting therapy and grade 3 headache. The number of patients experiencing permanent discontinuations of the study treatment due to adverse events was six in 1080 patients (0.6%) in the pooled LDV/SOF arms and seven in 872 patients (0.8%) in the pooled LDV/SOF plus RBV arms. No treatment emergent deaths occurred.

For patients treated with LDV/SOF plus RBV, phase III results showed a higher incidence of adverse events for patients aged 65 years and over (90.3%) versus those aged less than 65 years (85.1%). The frequency of adverse events leading to study treatment discontinuation or interruption was higher in those aged 65 years or over (33.9%) versus those aged less than 65 years (12.0%).

Safety data from the double-blinded, placebo-controlled, phase II SIRIUS study allowed a comparison of side effects over 12 weeks. The safety profile of LDV/SOF and placebo was very similar although fatigue (occurring in 16.9% versus 3.8% patients) and headache (occurring in 35.1% versus 20.5% patients) were more frequent in the LDV/SOF arm than in the placebo arm[7].

The Committee for Medicinal Products for Human Use (CHMP) noted that the safety profile of LDV/SOF in patients with compensated liver disease due to HCV infection, and a calculated glomerular filtration rate (GFR) > 60 ml/min, was favourable. Although the safety data for patients with decompensated liver disease is non-comparative, LDV/SOF appeared well tolerated and no specific safety concerns had been identified[7].

3.7AWTTC critique

- The company has submitted LDV/SOF studies predominately covering treatment of patients with HCV genotype 1; with efficacy shown in treatment-naive and treatment-experienced patients with and without compensated cirrhosis or decompensated cirrhosis.
- The phase III studies did not include placebo or active comparator arms, the absence of which prevented direct or adjusted indirect comparison with other treatments. A naive comparison approach was taken to source efficacy data for comparators, taking data from individual studies and this was modelled in the economic evaluation. No further evaluation was provided in the clinical section of the company submission.
- In the Phase III studies, SVR rates were compared with an adjusted historical rate. Whether these historical rates are representative of current treatment strategies is less clear. In addition any confounding factors cannot be adequately assessed through the use of historical controls.
- The evidence for use of LDV/SOF in patients with HCV genotypes 3 and 4 is limited. The ongoing SYNERGY study analysed the treatment of 21 patients with genotype 4 infection. One phase II study (ELECTRON 2) involved a limited number of patients (n = 51) with HCV genotype 3[1]. CHMP note that LDV is likely to have clinically relevant activity against genotype 3, albeit lower than against genotype 1[7].
- LDV/SOF (Harvoni®▼) is an interferon and protease inhibitor free treatment. For the majority of genotype 1 patients it can be administered as a single tablet for 8-12 weeks providing a simplified dosing regimen as compared with interferon and protease based regimens[2,8,9]. In addition, interferon-based regimens can be associated with serious side effects that limit treatment effectiveness. Serious adverse events and discontinuation rates due to adverse events were low in the LDV/SOF clinical trials[7]. However the majority of the trials were open label which may impact on the reliability of these results.
- The results of the ongoing, open label, phase II ERADICATE study in patients coinfected with HIV and HCV genotype 1, indicate that HIV infection does not impact response to LDV/SOF[7]. SVR12 was achieved for 13 out of 13 treatment-naive patients and for 36 of 37 (97%) treatment-experienced patients[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS
4.1 Cost-effectiveness evidence

4.1.1 Context
The company submission[1] describes a cost-utility analysis (CUA) of LDV/SOF combination tablet in the treatment of adults with chronic HCV genotypes 1 or 4 only and who commence treatment when non-cirrhotic or with compensated cirrhosis; the analysis does not include those infected with genotype 3, or those commencing treatment when already experiencing decompensated cirrhosis or pre/post liver transplant, in whom LDV/SOF is also licensed[2]. Separate analyses for treatment experienced and treatment naive patients have been conducted. The comparators are:

- SOF+PEG-IFN+RBV, which is subject to ongoing appraisal by NICE
- SMV+PEG-IFN+RBV, which is subject to ongoing appraisal by NICE
- SMV+SOF (in patients who are unable to tolerate interferon containing regimens) which is subject to ongoing appraisal by NICE
- TVR+PEG-IFN+RBV (licensed for use in genotype 1 only)
- BOC+PEG-IFN+RBV (licensed for use in genotype 1 only)
- PEG-IFN+RBV
- No treatment (as the only treatment option for treatment experienced patients who previously failed a protease inhibitor [PI] regimen, or for any interferon ineligible population where NICE do not recommend an interferon-free regimen).

The analysis is based on a Markov model adapted from a previous NICE submission on SOF[1]. Chronic HCV patients, with baseline characteristics derived from the HCV UK research database and a previous Health Technology Analysis (HTA) report[18], can enter the model with either non-cirrhotic or compensated cirrhotic HCV and receive treatment with LDV/SOF or one of the comparators for a duration based on genotype and previous treatment history. Non-cirrhotic patients who achieve a SVR by 12 weeks following the end of treatment are effectively cured, while those who fail to achieve SVR are at risk of developing compensated cirrhosis and subsequent progression to decompensated cirrhosis, liver transplant, or hepatocellular carcinoma, and death. Those with compensated cirrhosis who achieve SVR are effectively cured of their HCV infection but remain at (reduced) risk of developing decompensated cirrhosis or hepatocellular carcinoma, while those who fail to achieve SVR are at full risk of progression. It is assumed that patients do not die and do not progress while on treatment or during the 12 or 24 weeks after the end of treatment, and recurrence and re-infection do not occur[1].

Probabilities of progression following treatment with LDV/SOF and the comparators are determined by SVR rates obtained from the three phase III trials of LDV/SOF in patients with virus genotype 1[15–17], comparator trials and SPCs for each population of relevance. As the three LDV/SOF trials only compared different LDV/SOF regimens against each other, no direct or adjusted indirect comparisons have been possible; therefore, the relative efficacy of LDV/SOF and comparators in the model is based on unadjusted (naive) indirect comparative data. It is assumed that efficacy in patients with virus genotype 4 is the same as in patients with genotype 1, and that efficacy is the same in patients co-infected with HIV as in those with HCV monoinfection[1]. Risks of progression to subsequent worse health states in those who do not achieve SVR are based on estimates from the literature, those adopted previous HTA reports[18–20] and expert opinion.

Utility values attached to health states are based on those used in previous HTA reports[18–20]. Utility decrements are included to reflect reduced quality of life due to adverse events whilst on RBV and PEG-IFN containing regimens, based on values adopted in previous NICE technology appraisals of chronic HCV treatments, or mapping of health-related quality of life scores from clinical trials. Patients achieving

SVR are assumed to have an absolute increase in utility of 0.04 over their pre-treatment baseline value, based on health-related quality of life changes observed in a trial of telaprevir conducted in treatment naive genotype 1 patients[21].

Resource use and costs related to patient monitoring, adverse event management and individual health states are based on previous HTA reports and expert opinion. Treatment costs are determined by assumed treatment durations and discontinuations, which are informed by those observed in clinical trials, SPC recommendations, and (for LDV/SOF) the baseline viral loads observed in data from the HCV UK research database[1].

A lifetime horizon of analysis (up to patient age 100 years) has been adopted, with costs and outcome beyond one year discounted at 3.5% per annum[1].

4.1.2 Results

The company's base case analyses consider non-cirrhotic and compensated cirrhotic patients together.

4.1.2.1 Genotype 1, treatment naive patients

Results in cirrhotic and non-cirrhotic patients combined, with virus genotype 1, who are treatment naive are presented in Table 3. Compared with no treatment, all treatment strategies had an incremental cost per QALY gained of less than £20,000. The basis of a strategy of no treatment in the entire population of treatment naive patients is unclear, but the company notes that a proportion of patients with genotype 1 who are not candidates for interferon-based regimens may currently have no other treatment options.

LDV/SOF generated the greatest number of QALYs of all the treatment strategies, and in the incremental analysis dominated all other treatment strategies (i.e. LDV/SOF was overall more effective and less costly) except PEG-IFN+RBV, against which LDV/SOF had an incremental cost per QALY gained of £7,985.

In all deterministic sensitivity analyses that were presented around the base case model, the estimated incremental cost per QALY gained for LDV/SOF versus all comparators remained below £20,000. The most common parameters to which the ICER estimates were most sensitive across the different comparators were: the annual discount rate assumed simultaneously on both costs and outcomes (explored in the range 0-6%), overall treatment costs for non-cirrhotic patients (drug acquisition, monitoring and adverse event costs explored collectively in the range +/-25%), and the transition probability for moving from non-cirrhotic to compensated cirrhosis health state (explored in the range +/-75%). The assumed SVR rates for SOF+PEG-IFN+RBV and for SMV+PEG-IFN+RBV (explored in the range of an estimated 95% confidence interval) were among the most influential assumptions in those comparisons with LDV/SOF. In probabilistic sensitivity analysis, the probability of LDV/SOF being the most cost effective treatment strategy at a willingness to pay of £20,000 per QALY was 100%.

Table 3. Base case CUA results in genotype 1, treatment naive patients (combined non-cirrhotic and cirrhotic patients)[1].

Treatment strategy	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus No treatment	Incremental analysis
No treatment	£18,956	18.30	13.01					
PEG-IFN2a+RBV	£25,308	19.23	13.98	£6,352	0.94	0.97	£6,548	£6,548
LDV/SOF	£38,713	20.81	15.66	£19,757	2.51	2.65	£7,458	£7,985
SMV+ PEG-IFN2a+RBV	£38,731	20.14	15.02	£19,774	1.84	2.01	£9,840	Dominated
TVR+PEG-IFN2a+RBV	£40,237	19.99	14.85	£21,281	1.70	1.84	£11,571	Dominated
BOC+PEG-IFN2b+RBV	£41,299	19.93	14.66	£22,342	1.63	1.65	£13,537	Dominated
SOF+ PEG-IFN2a+RBV	£45,776	20.54	15.40	£26,819	2.24	2.39	£11,215	Dominated
SOF+SMV	£65,630	20.74	15.57	£46,674	2.44	2.56	£18,204	Dominated

BOC, boceprevir; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

The company subsequently provided limited results of the base case analysis, broken down into patients with or without cirrhosis at baseline (Table 4). Under the same assumptions as the base case analysis above, the maximum ICER estimate reported by the company was £10,400 per QALY in non-cirrhotic patients when LDV/SOF was compared against PEG-IFN2a+RBV.

Table 4. Base case ICERs (LDV/SOF vs. comparators) in genotype 1, treatment naive patients by baseline cirrhosis status[1].

Comparator	Base case	Non-cirrhotic	Cirrhotic
SOF+PR	LDV/SOF dominates	LDV/SOF dominates	£1,349
SMV+PR	LDV/SOF dominates	LDV/SOF dominates	£3,156
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
BOC+PEG-IFN2b+RBV	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
TVR+PEG-IFN2a+RBV	LDV/SOF dominates	LDV/SOF dominates	£1,522
PEG-IFN2a+RBV	£7,985	£10,397	£4,731
No treatment	£7,458	£8,965	£4,920

BOC, boceprevir; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon + ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
LDV/SOF dominates = LDV/SOF is both more effective and less costly than the comparator.

4.1.2.2 Genotype 4, treatment naive patients

Results in cirrhotic and non-cirrhotic patients combined, with virus genotype 4, who are treatment naive are presented in Table 5. Compared with no treatment, all treatment strategies had an incremental cost per QALY gained of less than £20,000. However,

the basis of a strategy of no treatment in the entire population of treatment naive patients is unclear.

LDV/SOF generated the greatest number of QALYs of all the treatment strategies, and in the incremental analysis all other treatment strategies except PEG-IFN+RBV, were either dominated or extendedly dominated by LDV/SOF (i.e. LDV/SOF was either overall more effective and less costly than the comparators, or else provided more QALYs at an ICER within the usual threshold). Compared with PEG-IFN+RBV, LDV/SOF had an incremental cost per QALY gained of £12,715.

In deterministic sensitivity analyses that were presented, the most common parameters to which the ICER estimates were most sensitive across the different comparators were: the annual discount rate assumed simultaneously on both costs and outcomes (explored in the range 0-6%), overall treatment costs for non-cirrhotic patients (drug acquisition, monitoring and adverse event costs explored collectively in the range +/-25%), the transition probability for moving from non-cirrhotic to compensated cirrhosis health state (explored in the range +/-75%) and the assumed SVR rates for the comparators (explored in the range of an estimated 95% confidence interval). In non-cirrhotic patients, a 25% increase in the overall costs of LDV/SOF or a 25% decrease in the overall costs of SOF+PEG-IFN2a+RBV or SMV+PEG-IFN2a+RBV increased the ICER to £33-34,000 per QALY gained. In probabilistic sensitivity analysis, the probability of LDV/SOF being the most cost effective treatment strategy was reported as 88% at a willingness to pay of £20,000 per QALY gained and 100% at £30,000 per QALY gained.

Table 5. Base case CUA results in genotype 4, treatment naive patients (combined non-cirrhotic and cirrhotic patients)[1].

Treatment strategy	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus no treatment	incremental
No treatment	£18,956	18.30	13.01					
PEG-IFN2a+RBV	£25,308	19.23	13.98	£6,352	0.94	0.97	£6,548	£6,548
SMV+ PEG-IFN2a+RBV	£38,731	20.14	15.02	£19,774	1.84	2.01	£9,840	Extendedly dominated
SOF+ PEG-IFN2a+RBV	£45,776	20.54	15.40	£26,819	2.24	2.39	£11,215	Extendedly dominated
LDV/SOF	£46,823	20.81	15.67	£27,867	2.52	2.66	£10,468	£12,715
SOF+SMV	£65,630	20.74	15.57	£46,674	2.44	2.56	£18,204	Dominated

ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

The company subsequently provided limited results of the base case analysis, broken down into patients with or without cirrhosis at baseline (Table 6). Under the same assumptions as the base case analysis above, the maximum ICER estimate reported by the company was £23,100 per QALY in non-cirrhotic patients when LDV/SOF was compared against PEG-IFN2a+RBV.

Table 6. Base case ICERs (LDV/SOF vs. comparators) in genotype 4, treatment naive patients by baseline cirrhosis status[1].

Comparator	Base case	Non-cirrhotic	Cirrhotic
SOF+PR	£3,869	£6,790	£1,349
SMV+PR	£12,399	£23,136	£3,156
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	LDV/SOF dominates
PEG-IFN2a+RBV	£12,715	£18,555	£4,731
No treatment	£10,468	£13,734	£4,920

ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon+ ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.
LDV/SOF dominates = LDV/SOF is both more effective and less costly than the comparator.

4.1.2.3 Genotype 1 and 4, treatment experienced patients

Results in cirrhotic and non-cirrhotic patients combined, with virus genotype 1 and 4, who are treatment experienced, are presented in Table 7. Compared with no treatment, LDV/SOF had the lowest incremental cost per QALY gained and generated the most QALYs; therefore, all other treatment strategies were either dominated or extendedly dominated by LDV/SOF (i.e. LDV/SOF was either overall more effective and less costly than the comparators, or else provided more QALYs at a lower ICER within the usual threshold). Compared with no treatment, LDV/SOF had an incremental cost per QALY gained of £13,527.

In deterministic sensitivity analyses that were presented, the most common parameters to which the ICER estimates were most sensitive across the different comparators were: the annual discount rate assumed simultaneously on both costs and outcomes (explored in the range 0-6%), overall treatment costs for non-cirrhotic patients (drug acquisition, monitoring and adverse event costs explored collectively in the range +/-25%), the transition probability for moving from non-cirrhotic to compensated cirrhosis health state (explored in the range +/-75%) and the assumed SVR rates for the comparators (explored in the range of an estimated 95% confidence interval). In non-cirrhotic patients, a 25% increase in the overall costs of LDV/SOF or a 25% decrease in the overall costs of SOF+PEG-IFN2a+RBV or SMV+PEG-IFN2a+RBV increased the ICER to £22-25,000 per QALY gained. In probabilistic sensitivity analysis, the probability of LDV/SOF being the most cost effective treatment strategy was reported as 88% at a willingness to pay of £20,000 per QALY gained and 100% at £30,000 per QALY gained.

A scenario analysis has been conducted exploring the impact of assuming all treatment experienced patients with virus genotype 1 and 4 and compensated cirrhosis are treated with LDV/SOF plus RBV for 12 weeks instead of LDV/SOF for 12 or 24 weeks. This is based on data from the phase II SIRIUS trial, which observed similar rates of SVR with LDV/SOF plus ribavirin for 12 weeks and LDV/SOF for 24 weeks in treatment experienced patients with genotype 1 and compensated cirrhosis[22]. Results are very similar to the base case analysis in patients with virus genotype 1 and 4 who are treatment experienced, because only a small proportion of patients (~5%) are modelled to receive LDF/SOF treatment for 24 weeks in the base case analysis[1]. However, the current SPC for LDV/SOF does not include LDV/SOF plus RBV as a recommended treatment strategy in patients with virus genotype 1 and 4 and compensated cirrhosis[2].

Table 7. Base case CUA results in genotype 1 and 4, treatment experienced patients (combined non-cirrhotic and cirrhotic patients)[1].

Treatment strategy	Total			Incremental			ICER (£)	ICER (£)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	versus no treatment	incremental
No treatment	£18,143	17.44	12.40					
PEG-IFN2a+RBV	£24,960	17.83	12.75	£6,817	0.39	0.35	£19,292	Extended dominance
TVR+PEG-IFN2a+RBV†	£42,101	18.84	13.90	£23,959	1.40	1.51	£15,890	Extended dominance†
SMV+ PEG-IFN2a+RBV	£43,626	19.17	14.13	£25,483	1.73	1.73	£14,740	Extended dominance
BOC+PEG-IFN2b+RBV†	£45,897	18.62	13.69	£27,754	1.18	1.30	£21,419	Dominated†
SOF+ PEG-IFN2a+RBV	£46,756	19.16	14.21	£28,613	1.72	1.81	£15,765	Extended dominance
LDV/SOF	£49,537	19.58	14.72	£31,395	2.13	2.32	£13,527	£13,527
SOF+SMV	£64,720	19.60	14.71	£46,577	2.16	2.31	£20,166	Dominated

BOC, boceprevir; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LYG, life years gained; PEG-IFN, pegylated interferon; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir; GT: genotype.
† TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV are relevant for GT1 HCV only as they are not licensed for the treatment of GT4 HCV

The company subsequently provided limited results of the base case analysis, broken down into patients with or without cirrhosis at baseline (Table 8). Under the same assumptions as the base case analysis above, LDV/SOF was both more effective and less costly, or had an ICER less than £20,000 per QALY gained compared against all comparators except SMV+SOF in patients with cirrhosis, against which LDV/SOF was both less effective and less costly.

Table 8. Base case ICERs (LDV/SOF vs. comparators) in genotype 1 and 4, treatment experienced patients by baseline cirrhosis status[1].

Comparator	Base case	Non-cirrhotic	Cirrhotic
SOF+PR	£5,497	£3,011	£11,001
SMV+PR	£9,984	£10,494	£9,102
SMV+SOF	LDV/SOF dominates	LDV/SOF dominates	SW quadrant
BOC+PEG-IFN2b+RBV†	£3,551	£5,748	£1,265
TVR+PEG-IFN2a+RBV†	£9,144	£13,741	£4,303
PEG-IFN2a+RBV	£12,491	£16,125	£6,666
No treatment	£13,527	£17,205	£7,415

BOC, boceprevir; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; PEG-IFN, pegylated interferon; PR, pegylated interferon + ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.
LDV/SOF dominates = LDV/SOF is both more effective and less costly than the comparator.
SW Quadrant =LDV/SOF is both less costly and less effective than SMV+SOF

4.1.3 AWTTC critique

There is a lack of comparative trial data for LDV/SOF. The economic model therefore relies on unadjusted, indirect comparisons of trial data to model the efficacy of LDV/SOF versus the comparators, which are subject to significant uncertainties and potential bias. The company assumes the large majority of patients in each modelled population will receive the shortest LDV/SOF treatment durations possible, based on a range of sources and expert opinion. The base case analyses are blended analyses that combine cirrhotic and non-cirrhotic patient populations into single analyses. The company has subsequently provided ICER estimates for these populations separately; however, the deterministic and probabilistic sensitivity analyses combine cirrhotic and non-cirrhotic patients as blended analyses, which reduces transparency to explore differential effects of key assumptions.

Collectively, the base case analyses appear subject to considerable uncertainty, and it is therefore not clear the analyses would reflect the cost effectiveness of the use of LDV/SOF in practice.

Key strengths of the economic evidence include:

- The model is based on adaptation of models of chronic HCV treatment accepted in previous HTA reports and recently submitted to NICE.
- A wide range of deterministic sensitivity analyses have been conducted.

Key limitations and uncertainties in the economic evidence include:

- There are no direct comparative trial data for LDV/SOF and other treatment strategies, and the lack of a common comparator arm in the trials precludes adjusted indirect treatment comparisons. The efficacy of LDV/SOF and comparators in the model is therefore based on simple, unadjusted SVR rates obtained from trials, which are observational in nature and subject to significant uncertainty and potential bias.
- Clinical data to support the use of LDV/SOF in patients with virus genotype 4 are limited[2]. It is assumed that data for treatment of patients with virus genotype 1 can be generalised to patients with virus genotype 4. The company submission states that scenario analyses have been run applying genotype 4-specific SVR data for LDV/SOF and comparators, but these appear not to have been presented.
- The base case analyses reflect blended analyses that combine clinically distinct cirrhotic and non-cirrhotic patient groups together. The company has subsequently provided limited results of base case analyses in these patients groups separately; however, sensitivity analyses lack transparency to determine differential impacts of key assumptions in the model:
    - Overall costs of treatment strategies (incorporating drug acquisition, monitoring and adverse event costs) are varied within a range of +/-25%, and demonstrate that treatment costs for non-cirrhotic patients are among the most influential parameters in all comparisons, particularly in treatment experienced patients and patients with virus genotype 4 where, from a base case of dominance, ICERs in excess of £20,000 per QALY gained are produced. However, analyses specifically exploring the impact of the assumed proportion of patients with cirrhotic or non-cirrhotic disease, and within that the proportions requiring the minimum and maximum recommended treatment durations are not presented.
    - Alternative scenarios for comparator treatment durations are not considered (e.g. PEG-IFN2a+RBV is assumed in the model to be given for 48 weeks in patients with virus genotype 1, but the SPC indicates 24 weeks may be possible in those with low viral load who achieve and maintain viral clearance at weeks 4 and 24[23]).
- Scenario analysis is limited to exploration of the use of a 12 week course of LDV/SOF plus RBV in treatment experienced patients with virus genotype 1

and 4 and compensated cirrhosis. The company reports that expert opinion indicates this regimen may be used in practice; however, this is not a recommended regimen in the current SPC[2].

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost effectiveness of LDV/SOF relevant to the UK NHS.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Public Health Wales data, approximately 12,000 people have chronic HCV , of which only a quarter are aware[5]. Of these, the company estimates around 50% have virus genotype 1 or 4, equivalent to 1,500 people in Wales. It is assumed that this number remains constant as the number of newly diagnosed cases is approximately equal to the number successfully treated. Based on Public Health data 2011-12[24], the company assumes 400 patients are treated in Wales each year, of which 200 are assumed to have virus genotype 1 or 4. The company anticipates treatment rates will rise as a result of the introduction of LDV/SOF because it provides a shorter, interferon-free regimen compared to current treatment options. Based on the uptake in other European countries, the company anticipates the number of people prescribed LDV/SOF would be no more than double previous treatment rates (maximum 400 per year), and assumes uptake rates [commercial in confidence data removed] in each of the next 5 years, equivalent to [commercial in confidence data removed] people to be treated with LDV/SOF in each of the next 5 years[1].

The company anticipates differential levels of displacement of comparator treatment strategies based on genotype, but [commercial in confidence data removed].

5.1.2 Results

The company estimates the net budget impact in Wales in each of the next five years, taking account of acquisition costs only, as in Table 6.

Table 6. Company estimates of net cost implications associated with use of LDV/SOF[1]

	Year 1	Year 2	Year 3	Year 4	Year 5
LDV/SOF acquisition cost per patient per annum	£34,001	£34,001	£34,001	£34,001	£34,001
Displaced medicines cost per patient per annum	-£34,108	-£34,108	-£34,108	-£34,108	-£34,108
Net additional medicines savings/costs	-£107	-£107	-£107	-£107	-£107
Number of eligible patients	400	400	400	400	400
Number of patients treated in each year	*	*	*	*	*
Net total budget impact	**-£17,057**	**-£21,322**	**-£19,189**	**-£12,793**	**-£6,396**
***** commercial in confidence data removed					

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the number of patients eligible for treatment with LDV/SOF. The same proportions of patients are assumed to receive treatment for the same durations as in the economic model.
- The company assumes reduced uptake in year 2 as a result of new market entrants. Estimates of uptake are subject to uncertainty as in all budget impact analyses.

- No exploration of alternative scenarios and assumptions have been provided.

5.2 Comparative unit costs

The cost per course of treatment with LDV/SOF and the comparators is dependent upon patients' treatment histories, infecting virus genotypes, baseline viral load, and cirrhotic states. Table 7 therefore provides only illustrative examples of the magnitude of costs per course of treatment with LDV/SOF and alternative treatment strategies based on relevant SPC-recommended treatment durations for monoinfected patients who are eligible for interferon based regimens, and SOF+SMV for those ineligible for interferon-based therapy.

Table 7. Example costs per course of treatment with LDV/SOF and alternative chronic HCV treatment regimens

Regimen	GT1, TN, non-cirrhotic	GT 1, TE, compensated cirrhosis	GT 3, cirrhotic and/or TE
LDV/SOF	8 or 12 weeks £25,987 to £38,980	12 or 24 weeks £38,980 to £77,960	24 weeks £77,960
PEG-IFN2a+RBV	24 or 48 weeks £4,914 to £9,828	48 weeks £9,828	16 or 24 weeks £3,276 to £4,914
SMV+ PEG-IFN2a+RBV	24 weeks £27,312	24 or 48 weeks £27,312 to £32,226	n/a
SOF+ PEG-IFN2a+RBV	12 weeks £37,440	12 weeks £37,440	12 weeks £37,440
SOF+SMV	12 weeks £57,381	12 weeks £57,381	n/a
BOC+PEG-IFN2a+RBV	28 or 48 weeks £22,533 to £40,628	48 weeks £40,628	n/a
TVR+PEG-IFN2a+RBV	24 or 48 weeks £27,312 to £32,226	48 weeks £32,226	n/a

Costs based on BNF list prices[25] except LDV/SOF based on company information. Assumes adult weight of 79kg as per the company's economic model and no discontinuations.
This table does not imply therapeutic equivalence of drugs or doses.
See relevant Summaries of Product Characteristics for full dosing details[2,10,23,26–29].

GT: genotype; TN: treatment-naive; TE: treatment-experienced; BOC, boceprevir; LDV, ledipasvir; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir.

Costs for 12 or 24 weeks LDV/SOF also apply to patients with virus genotype 4. NB: TVR+PEG-IFN2a+RBV and BOC+PEG-IFN2a+RBV not licensed for the treatment of virus genotype 4 HCV

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, LDV/SOF (Harvoni®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that LDV/SOF (Harvoni®▼) would be supplied by a home healthcare provider. This service is already in place; a choice of two service providers is currently available[1].

6.2 Ongoing studies

In addition to the ongoing phase II studies discussed above the company highlighted four additional studies that are likely to be available within 6–12 months:

- ION 4 (GS-US-337-0115) is a phase III study of patients with HCV genotypes 1 or 4, with HIV confection and with either no cirrhosis or with compensated cirrhosis treated with LDV/SOF for 12 weeks[30].
- SOF re-treatment (GS-US-337-1118) is a study of SOF-experienced patients with HCV genotype 1 treated with LDV/SOF with and without RBV for either 12 or 24 weeks[31].
- SOLAR 2 (GS-US-337-0124) is a study of patients with HCV genotypes 1 or 4, either post-liver transplant or with advanced liver disease treated with LDV/SOF plus RBV for either 12 or 24 weeks[32].
- GS-US-337-1119 is a phase II study of naive and treatment-experienced patients with HCV genotypes 4 or 5, with either no cirrhosis or with compensated cirrhosis,treated with LDV/SOF[33].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search:18 December 2014.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Child Pugh Turcotte (CPT) classification for liver cirrhosis

The CPT system provides a classification of cirrhosis with severity increasing from class A to class B to class C[34].

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