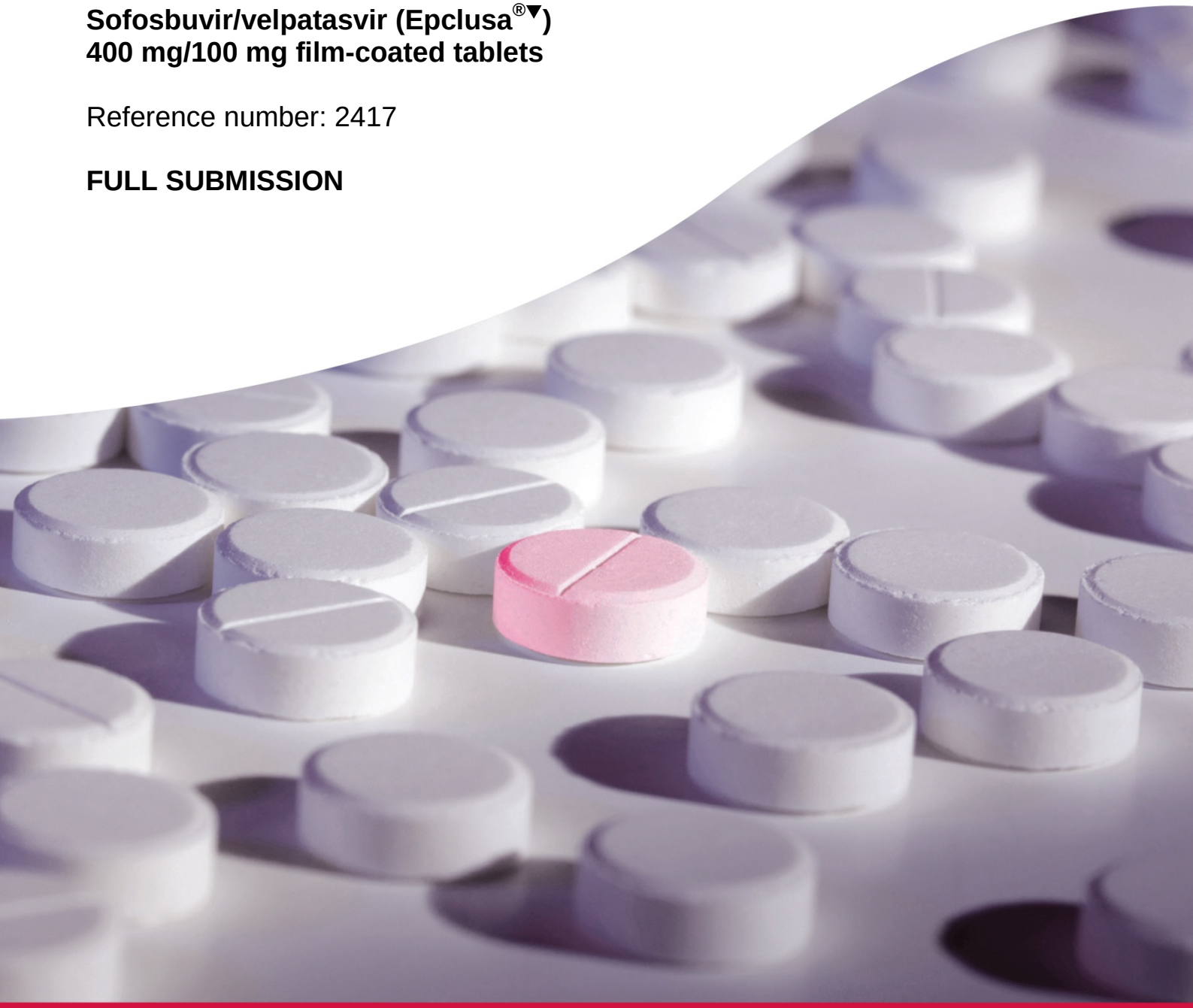
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Sofosbuvir/velpatasvir (Epclusa®▼) 400 mg/100 mg film-coated tablets

Reference number: 2417

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Sofosbuvir/velpatasvir (Epclusa®▼) 400 mg/100 mg film-coated tablets

This assessment report is based on evidence identified from a literature search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) and information provided by Gilead Sciences Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Sofosbuvir/velpatasvir (Epclusa®▼) for the treatment of chronic hepatitis C virus (HCV) infection in adults[2]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions[2].
Dosing	For patients without cirrhosis and patients with compensated cirrhosis the recommended dose is one sofosbuvir/velpatasvir 400 mg/100 mg tablet, taken orally, once daily for 12 weeks[2]. The addition of ribavirin may be considered for people with genotype 3 hepatitis C virus infection who have compensated cirrhosis[2]. For patients with decompensated cirrhosis the recommended dose is one sofosbuvir/velpatasvir 400 mg/100 mg tablet, taken orally, once daily for 12 weeks with ribavirin dosed according to Child-Pugh-Turcotte (CPT) class and transplant status[2]. Refer to the Summary of Product Characteristics (SPC) for further information regarding dosing.
Marketing authorisation date	6 July 2016[2]
UK launch date	July 2016

2.0 DECISION CONTEXT

2.1 Background

Hepatitis C virus (HCV) is a blood-borne virus that causes liver inflammation and affects liver function[3]. It is one of the main causes of chronic liver disease[4]. Around 20% of people infected with HCV naturally clear the infection within six months, but most people will develop chronic hepatitis C which may be life-long[5]. Around 30% of people develop cirrhosis, or severe scarring of the liver[3]. The mean time to development of cirrhosis is estimated at 20 years; although only 10–20% of people will develop cirrhosis within the first 20 years[6]. Compensated cirrhosis means that the liver is still able to function but over time, without treatment, this will progress to decompensated cirrhosis (DCC) when the remaining liver is unable to compensate for the loss of function[7]. The risk of developing liver cancer is relatively small; around 2-4% of people with cirrhosis will develop liver cancer per year[8].

The prevalence of HCV infection is difficult to establish because many people are asymptomatic and unaware of their infection[3]. In Wales there were 480 laboratory reports of HCV infection in 2012; most were in males aged 25–49 years[9]. It has been

estimated that 12,000 to 14,000 people in Wales have chronic HCV infection[10]. There are six main genotypes of HCV. A 2013 report estimated that around 215,000 people in the UK have chronic HCV infection and most infections (around 90%) are caused by HCV genotype 1 and HCV genotype 3[9].

The aim of treatment is to cure the HCV infection[4]. Sustained virologic response (SVR) is defined as an undetectable HCV RNA 12 weeks (SVR_{12}) or 24 weeks (SVR_{24}) after the end of treatment. The infection is cured in more than 99% of people who achieve an SVR. The SVR is generally associated with resolution of liver disease in people without cirrhosis, although those with cirrhosis remain at risk of life-threatening complications[4].

HCV genotype influences response to treatment[3]. Table 1 lists treatments for each genotype as recommended by National Institute for Health and Care Excellence (NICE) guidance on chronic hepatitis C. See Appendix 1 for a detailed table of each recommended treatment regimen dependent on HCV genotype for people who are treatment-naive or treatment-experienced, and with or without cirrhosis.

Table 1. HCV treatments recommended by NICE

HCV genotype	Recommended treatments	NICE guidance
Genotype 1	Peginterferon alfa and ribavirin	TA 200
	Telaprevir	TA 252
	Boceprevir	TA 253
	Simeprevir	TA 331
	Ledipasvir/sofosbuvir	TA 363
	Sofosbuvir	TA 330
	Daclatasvir	TA 364
	Ombitasvir/paritaprevir/ritonavir	TA 365
Genotype 2	Peginterferon alfa and ribavirin	TA 200
	Sofosbuvir	TA 330
Genotype 3	Peginterferon alfa and ribavirin	TA 200
	Sofosbuvir	TA 330
	Daclatasvir	TA 364
Genotype 4	Peginterferon alfa and ribavirin	TA 200
	Simeprevir	TA 331
	Ledipasvir/sofosbuvir	TA 363
	Daclatasvir	TA 364
	Ombitasvir/paritaprevir/ritonavir	TA 365
	Sofosbuvir	TA 330
Genotypes 5 & 6	Peginterferon alfa and ribavirin	TA 200
	Sofosbuvir	TA 330
HCV: hepatitis C virus; TA: technology appraisal		

Sofosbuvir/velpatasvir (Epclusa®) is an oral fixed-dose combination of two direct-acting antivirals: 400 mg sofosbuvir and 100 mg velpatasvir; both have pan-genotypic activity against HCV genotypes 1–6[2]. Sofosbuvir inhibits the HCV non-structural protein 5B (NS5B) RNA-dependent RNA polymerase which is essential for viral replication. Velpatasvir inhibits the NS5A protein, which is essential for RNA replication and assembly of HCV virions[2].

2.2 Comparators

Current treatments for hepatitis C in Wales[3]:

- ledipasvir/sofosbuvir (Harvoni®)
- daclatasvir (Daklinza®) plus sofosbuvir (Sovaldi®)
- daclatasvir (Daklinza®) plus sofosbuvir (Sovaldi®) plus ribavirin
- daclatasvir (Daklinza®) plus peginterferon plus ribavirin
- sofosbuvir (Sovaldi®) plus ribavirin
- sofosbuvir (Sovaldi®) plus ribavirin plus peginterferon alfa
- ombitasvir/paritaprevir/ritonavir (Viekirax®)

- ombitasvir/paritaprevir/ritonavir (Viekirax®) plus dasabuvir (Exviera®) or ribavirin
- simeprevir (Olysio®) plus peginterferon alfa plus ribavirin
- boceprevir (Victrelis®) plus peginterferon alfa plus ribavirin
- telaprevir (Incivo®) plus peginterferon alfa plus ribavirin
- peginterferon alfa plus ribavirin
- peginterferon alfa.

2.3 Guidance and related advice

- NICE Technology Appraisal in development. Elbasvir-grazoprevir for treating chronic hepatitis C [ID842]. Publication expected January 2017[11]
- NICE Technology Appraisal in development. Sofosbuvir-velpatasvir for treating chronic hepatitis C [ID 921]. Publication expected January 2017[3]
- World Health Organization (2016) Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection[8]
- European Association for the Study of the Liver (EASL) clinical practice guidelines (2015) Recommendations on treatment of hepatitis C 2015[4]
- NICE Technology Appraisal (TA) 365 (2015) Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C[12]
- NICE TA364 (2015) Daclatasvir for treating chronic hepatitis C[13]
- NICE TA363 (2015) Ledipasvir–sofosbuvir for treating chronic hepatitis C[14]
- NICE TA331 (2015) Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C[15]
- NICE TA330 (2015) Sofosbuvir for treating chronic hepatitis C[16]
- SIGN guideline 133 (2013) Management of hepatitis C[17]
- NICE TA253 (2012) Boceprevir for the treatment of genotype 1 chronic hepatitis C[18]
- NICE TA252 (2012) Telaprevir for the treatment of genotype 1 chronic hepatitis C[19]
- NICE TA200 (2010) Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C[20]

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of ledipasvir/sofosbuvir (Harvoni®)[21] and for daclatasvir (Daklinza®)[22].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A literature search conducted by AWTTC identified four phase III studies (ASTRAL–1 to 4) of the fixed dose combination of sofosbuvir/velpatasvir conducted in people with HCV infection caused by genotypes 1–6. The company's submission included these four ASTRAL studies as well as some preliminary data from the ASTRAL–5 study in people co-infected with HCV and HIV[1]. ASTRAL–1 was a double-blind study of sofosbuvir/velpatasvir compared with placebo in the treatment of HCV genotype 1,2,4,5 and 6 infections[23]. ASTRAL–2 and ASTRAL–3 were open-label studies of sofosbuvir/velpatasvir compared with sofosbuvir plus ribavirin in people with HCV genotype 2 and 3 infections[24]. ASTRAL–4 was an open-label study that compared three different treatment regimens of sofosbuvir/velpatasvir, including one in combination with ribavirin, in people with HCV genotypes 1–4 and 6[25]. The primary efficacy end point was the same in all ASTRAL trials: the rate of sustained virologic response (SVR), defined as an HCV RNA level < 15 IU/ml at 12 weeks after the end of treatment. The company did a systematic literature review and a network meta-analysis (NMA), although the results were not robust enough for use in the economic model and so are not included here.

3.1 ASTRAL–1 study

This international study enrolled 741 patients aged ≥ 18 years with chronic HCV infection caused by genotypes 1, 2, 4, 5 or 6[23]. Most patients (51%) were enrolled in Europe. The study included patients (around 20%) with compensated cirrhosis; patients with hepatic decompensation or hepatocellular carcinoma were excluded. Around 30% of patients had previously been treated for HCV infection with an interferon-based regimen but not with a NS5B or NS5A inhibitor.

Patients were randomly assigned in a 5:1 ratio to receive either a fixed-dose combination tablet of 400 mg sofosbuvir/100 mg velpatasvir taken orally once daily for 12 weeks (n = 589) or a placebo tablet for 12 weeks (n = 116). Randomisation was stratified by genotype and the presence or absence of cirrhosis. There were 35 patients with genotype 5 who did not undergo randomisation and were assigned to receive 12 weeks of treatment with sofosbuvir/velpatasvir. In total, 624 patients were assigned to the sofosbuvir/velpatasvir group.

The primary efficacy end point was the rate of SVR; secondary end points included rate of adverse events and treatment discontinuations. The SVR rates are shown in Table 2. Overall, 99% of patients treated with sofosbuvir/velpatasvir for 12 weeks had SVR compared with 0% of placebo-treated patients. This was significantly superior to the prespecified performance goal of 85% ($p < 0.001$)[23]. The SVR rates were > 99% in the subgroups of people with cirrhosis (n = 121) and people with previous treatment experience (n = 201) who were treated with sofosbuvir/velpatasvir[23].

Table 2. ASTRAL–1 study: primary and secondary end points

	400 mg sofosbuvir/100 mg velpatasvir (n=624)	placebo (n=116)
SVR% (95% CI)		
Any genotype	99 (98 to > 99)	0
Genotype 1a	98 (95 to > 99)	0
Genotype 1b	99 (95 to 100)	0
Genotype 2	100 (97 to 100)	0
Genotype 4	100 (97 to 100)	0
Genotype 5	97 (85 to > 99)	n/a
Genotype 6	100 (91 to 100)	0
Number of virologic failures		
During treatment	0	n/a
After treatment	2	n/a
Number of discontinuations, adverse events		
Discontinuation of treatment because of adverse event	1	2
Serious adverse event	15	0
CI: confidence interval; HCV: hepatitis C virus; n/a: not applicable; SVR: sustained virologic response rate, defined as HCV RNA < 15 IU/ml at 12 weeks after end of treatment		

Four health-related quality of life (HRQL) questionnaires were used in ASTRAL-1 to assess the effect of treatment on patient-reported outcomes: SF-36, chronic liver disease questionnaire for hepatitis C (CLDQ-HCV), functional assessment of chronic illness therapy – fatigue (FACIT-F) and work productivity and activity impairment (WPAI). Improvements in health-related quality of life in patients treated with sofosbuvir/velpatasvir were generally observed across all four tools between baseline and post-treatment week 12 which were significantly better than placebo ($p < 0.05$)[1].

3.2 ASTRAL–2 and ASTRAL–3

These two studies enrolled patients with HCV genotype 2 infection (ASTRAL–2) and genotype 3 infection (ASTRAL–3)[24]. ASTRAL–2 enrolled 269 patients at sites in the USA; ASTRAL–3 enrolled 558 patients in the USA, Canada, Europe, Australia and New Zealand. The studies included patients with compensated cirrhosis but not patients with hepatic decompensation or hepatocellular carcinoma, and included previously treated patients. The ASTRAL–3 study had larger percentages of patients who had cirrhosis (29-30%) and who had undergone unsuccessful treatment (26%).

Patients were randomly assigned in a 1:1 ratio to receive either a fixed-dose combination tablet of 400 mg sofosbuvir/100 mg velpatasvir taken orally once daily for 12 weeks, or 400 mg sofosbuvir plus ribavirin for 12 weeks (ASTRAL–2) or 24 weeks (ASTRAL–3). Ribavirin was administered orally twice daily at doses determined by body weight.

The primary efficacy end point was the rate of SVR, shown in Table 3. In ASTRAL–2, the rate of SVR at 12 weeks was 99% of sofosbuvir/velpatasvir-treated patients, compared with 94% of patients treated with sofosbuvir plus ribavirin. In ASTRAL–3, the rate of SVR at 12 weeks was 95% of sofosbuvir/velpatasvir-treated patients compared with 80% of those treated with sofosbuvir plus ribavirin for 24 weeks. There was a higher rate of virologic failure in ASTRAL–3: 11 patients (4%) in the sofosbuvir/velpatasvir group and 38 patients (14%) in the sofosbuvir plus ribavirin group. In ASTRAL–3, the rate of SVR was 88% among patients who had HCV NS5A resistance-associated variants at baseline and 97% in patients who did not have these variants[24]. The SVR rate was 91% among the 29% of patients treated with sofosbuvir/velpatasvir who had cirrhosis, and 89% among the 26% who had cirrhosis and had received previous treatment[24].

Table 3. ASTRAL–2 and ASTRAL–3 studies: primary and secondary end points

	ASTRAL–2 (HCV genotype 2)		ASTRAL–3 (HCV genotype 3)	
	sofosbuvir/velpatasvir for 12 weeks	sofosbuvir plus ribavirin for 12 weeks	sofosbuvir/velpatasvir for 12 weeks	sofosbuvir plus ribavirin for 24 weeks
	(n=134)	(n=132)	(n=277)	(n=275)
Primary end point				
SVR at 12 weeks %(95% CI)	99 (96 to 100)	94 (88 to 97)	95 (92 to 98)	80 (75 to 85)
Secondary end points				
Number of virologic failures (%)				
During treatment	0	0	0	1 (< 1)
After treatment	0	6 (5)	11 (4)	38 (14)
Number of discontinuations, adverse events (%)				
Discontinuation of treatment because of adverse event	1 (1)	0	0	9 (3)
Serious adverse event	2 (1)	2 (2)	6 (2)	15 (5)

CI: confidence interval; HCV: hepatitis C virus; SVR: sustained virologic response rate, defined as HCV RNA <15 IU/ml at 12 weeks after end of treatment

HRQL questionnaires were used in ASTRAL-2 and ASTRAL-3 to assess the effect of treatment on patient-reported outcomes: SF-36, CLDQ-HCV, FACIT-F and WPAI[1]. No on-treatment decrements in health-related quality of life were seen in the patients treated with sofosbuvir/velpatasvir-for 12 weeks; mean scores for most scales improved from end of treatment to post-treatment weeks 4 and 12[1].

3.3 ASTRAL–4

This study was conducted in the USA and enrolled 268 patients with chronic HCV infection of any genotype who had DCC classified as Child-Pugh-Turcotte class B (a score of 7–9 on a scale of 5–15 where higher values show more advanced disease)[25]. HCV genotypes were: 1a (n = 159), 1b (48), 2 (12), 3 (39), 4 (8) and 6 (1). Overall, 55% of patients had received previous treatment for HCV infection, none were treated with a NS5B or NS5A inhibitor.

Patients were randomly assigned in a 1:1:1 ratio to receive either a fixed dose combination tablet of 400 mg sofosbuvir/100 mg velpatasvir given orally once daily for 12 weeks or 24 weeks, or sofosbuvir/velpatasvir plus ribavirin (administered orally twice daily at doses determined by body weight) for 12 weeks. Randomisation was stratified according to HCV genotype; in each treatment group most (> 75%) patients had HCV genotype 1.

The primary efficacy end point was the rate of SVR. The study was not designed or powered to detect significant differences in rates of SVR among the different treatment groups. The SVR rates are shown in Table 4. Overall, the rate of SVR at 12 weeks was 83% of patients treated with sofosbuvir/velpatasvir for 12 weeks, 86% of those who received sofosbuvir/velpatasvir for 24 weeks, and 94% of patients treated with sofosbuvir/velpatasvir plus ribavirin for 12 weeks[25]. Post-hoc analyses did not detect any significant differences in rates of SVR among the three treatment groups[25].

Table 4. ASTRAL–4 study: primary and secondary end points

	sofosbuvir/velpatasvir for 12 weeks (n=90)	sofosbuvir/velpatasvir for 24 weeks (n=90)	Sofosbuvir/velpatasvir plus ribavirin for 12 weeks (n=87)
SVR% (95% CI)			
Any genotype	83 (74 to 90)	86 (77 to 92)	94 (87 to 98)
Genotype 1a	88 (76 to 96)	93 (82 to 98)	94 (85 to 99)
Genotype 1b	89 (65 to 99)	88 (62 to 98)	100 (77 to 100)
Genotype 2	100 (40 to 100)	75 (19 to 99)	100 (40 to 100)
Genotype 3	50 (23 to 77)	50 (21 to 79)	85 (55 to 98)
Genotype 4	100 (40 to 100)	100 (16 to 100)	100 (16 to 100)
Genotype 6	0 (n/a)	100 (3 to 100)	0 (n/a)
Number of virologic failures (%)			
All genotypes	11 (12)	8 (9)	3 (3)
Genotype 1a	3 (6)	2 (4)	1 (2)
Genotype 1b	2 (11)	1 (6)	0
Genotype 3	6 (43)	5 (42)	2 (15)
Number of discontinuations, adverse events (%)			
Discontinuation of treatment because of adverse event	1 (1)	4 (4)	4 (5)
Serious adverse event	17 (19)	16 (18)	14 (16)
CI: confidence interval; HCV: hepatitis C virus; n/a: not applicable; SVR: sustained virologic response rate, defined as HCV RNA < 15 IU/ml at 12 weeks after end of treatment			

3.4 ASTRAL-5

This open-label, single-arm phase III study evaluated the safety and efficacy of sofosbuvir/velpatasvir in 106 patients with HCV and HIV coinfection[26]. Eligibility criteria

were: co-infection with HIV and HCV (genotypes 1-6); being on stable antiretroviral therapy for > 8 weeks with CD4 counts ≥ 100 cells/mm^3; and having HIV RNA ≤ 50 copies/ml. Most patients (73%) had HCV genotype 1a or 1b infection, 19 (18%) had cirrhosis and 31 (29%) were treatment-experienced. All were treated with sofosbuvir/velpatasvir for 12 weeks; the primary end point was the rate of SVR at 12 weeks after treatment (SVR12)[26].

Preliminary results were reported for 104 patients (2 patients were pending SVR12 visit) and are shown in Table 5[1]. SVR12 was achieved by 99 patients (95%) and sofosbuvir/velpatasvir was safe and well tolerated with ART, including tenofovir disoproxil fumarate-based with boosted regimens[1].

Table 5. Preliminary results from ASTRAL-5, stratified by subgroup[1]

	n (total)	SVR12
Genotype		
Genotype 1a	62 (65)	95%
Genotype 1b	11 (12)	92%
Genotype 2	11 (11)	100%
Genotype 3	11 (12)	92%
Genotype 4	4 (4)	100%
Cirrhosis status		
Without cirrhosis	80 (85)	94%
With cirrhosis	19 (19)	100%
Treatment history		
Treatment-naïve	71 (75)	93%
Treatment-experienced	28 (29)	97%
SVR12: sustained virologic response rate, defined as HCV RNA < 15 IU/ml at 12 weeks after end of treatment		

3.5 Comparative safety

The most common adverse events reported in the ASTRAL studies were fatigue, headache, nausea, insomnia and nasopharyngitis[23-25]. In ASTRAL–1 there was no significant difference between the rates of any adverse event in patients treated with sofosbuvir/velpatasvir compared with those treated with placebo[23]. In the ASTRAL–2 and ASTRAL–3 studies the rates of adverse events were lower among patients treated with sofosbuvir/velpatasvir than in those treated with sofosbuvir plus ribavirin[24]; there was a higher frequency of fatigue and anaemia in patients treated with sofosbuvir plus ribavirin than in patients treated with sofosbuvir/velpatasvir[27]. In ASTRAL-3, patients treated for 24 weeks with sofosbuvir plus ribavirin had increased rates of insomnia, irritability and cough, which are all known to be associated with ribavirin treatment[24]. In ASTRAL–4 the most common serious adverse events were hepatic encephalopathy and sepsis, with each event occurring in 5 patients across the treatment groups[25].

Pooled phase III data from the ASTRAL studies showed that the proportion of patients who discontinued treatment because of adverse events was 0.2%, and 3.2% of patients experienced any severe adverse event[2]. Headache, fatigue and nausea were the most common treatment-emergent adverse events (with an incidence ≥ 10%). These were reported at a similar frequency in placebo-treated patients compared with patients treated with sofosbuvir/velpatasvir[2].

3.6 AWTTC critique

- The fixed-dose combination of sofosbuvir/velpatasvir (Epclusa®) is approved for use as monotherapy for treating hepatitis C, thereby offering a simplified treatment regimen that is ribavirin-free and interferon-free, similar to ledipasvir/sofosbuvir (Harvoni®). No studies have directly compared velpatasvir/sofosbuvir with ledipasvir/sofosbuvir or with daclatasvir. The

company conducted a NMA but results were only available for a proportion of NICE-approved treatments for HCV genotype 1 and genotype 3 treatment-naive infections and could not be broken down by treatment history, sub genotype or fibrosis stage.

- Sofosbuvir/velpatasvir has shown activity against all HCV genotypes. There are currently no interferon-free and ribavirin-free options recommended for treating HCV infection with genotypes 2, 4, 5 and 6 in people who are treatment-naive and do not have cirrhosis. For people with genotype 3 infection who are treatment-naive and without cirrhosis, daclatasvir plus sofosbuvir is only recommended if they have significant fibrosis[13].
- In the ASTRAL studies the rates of discontinuation and serious adverse effects were low[23-25]. However, only the ASTRAL–1 study was double-blinded, the remaining studies were open-label, which may introduce bias.
- The ASTRAL–2 and ASTRAL–3 studies compared sofosbuvir/velpatasvir with sofosbuvir plus ribavirin, and were powered to show non-inferiority rather than superiority[25].
- The ASTRAL–1 and ASTRAL–3 studies included patients in Europe and the study populations in all four ASTRAL studies were applicable to the population in Wales[23,24]. Each ASTRAL study included previously-treated patients: 32% of patients in ASTRAL–1, 15% in ASTRAL–2, 25% in ASTRAL–3 and 55% in ASTRAL–4. No patients in the studies had received previous treatment with a NS5A or NS5B inhibitor.
- Most patients in the ASTRAL-4 study had HCV genotype 1 infection, therefore there are very limited data in other genotypes for patients with DCC especially genotypes 2, 4 or 6. The ASTRAL-4 study enrolled only patients with moderate hepatic decompensation so the results are not generalisable to patients with more severe liver disease.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost utility analyses (CUA) comparing sofosbuvir/velpatasvir with a variety of comparators for the treatment of people with chronic hepatitis C[1]. Patient groups are defined by HCV genotype (GT), treatment experience (treatment-naive or treatment-experienced), and fibrosis status (non-cirrhotic, compensated cirrhosis or decompensated cirrhosis [DCC]). In addition, NICE has previously recommended some treatments only for people who are ineligible for IFN (IFNi). Therefore, separate economic analyses have been conducted to determine the cost-effectiveness of sofosbuvir/velpatasvir for all of these populations.

The CUA takes the form of a cohort Markov model, which represents an adaptation of a model designed by Dusheiko and Roberts[28]. It adopts an NHS/Personal Social Services perspective and a lifetime time horizon (age is capped at 100 years). The same model structure is used for all patients irrespective of HCV genotype or treatment experience. It consists of ten health states, with transition probabilities between the states. These states include: non-cirrhotic, compensated cirrhosis, DCC, sustained virologic response (SVR), non-cirrhotic, SVR: compensated cirrhosis, SVR:DCC, hepatocellular carcinoma (HCC), liver transplantation, post-liver transplant, and excess mortality. The model has two-week cycle lengths for the first 72 weeks, followed by 24-week cycle length for 24 weeks. Thereafter, transitions occur on an annual basis. Transition probabilities used in the model have been obtained from trials, Summaries of Product Characteristics (SPC), and the literature[29-34]; and in some instances assumptions have been made where subgroup specific probabilities are not available.
Patients enter the model in one of three health states: non-cirrhotic, compensated cirrhosis, or DCC. Patients then transition through the model in keeping with the natural

history of chronic hepatitis C, which has been informed by previous NICE submissions[14,16,35,36]. Patients can die in any health state. Age and gender specific general mortality rates are applied to each health state in the model. Still, the risk of death is highest in the most severe states, that is, DCC, HCC, liver transplant, and post-liver transplantation.

Given that the NMA conducted was not considered robust or credible for use in the economic model, naive comparisons were undertaken to inform clinical inputs. SVR rates, rates of adverse events and treatment durations were taken from the pivotal sofosbuvir/velpatasvir trials[23-25], comparator treatment trials, the literature and expert opinion.

The baseline quality of life for patients is defined by the health state in which they enter the model, and is measured using the EQ-5D tool. HRQL is assumed to remain constant in a health state, and to be the same for all patients in any given state regardless of how long they have been in that state. Values for health states have predominantly been taken from two trials[37,38]. On-treatment increments/decrements, which capture the effects of adverse events have been mapped to obtain SF-6D values for sofosbuvir/velpatasvir and comparators. Notably, sofosbuvir/velpatasvir and ledipasvir/sofosbuvir are associated with a 4.43% increment in the model (given lack of trial data for sofosbuvir/velpatasvir, equivalence has been assumed between these), while the other comparators are associated with decrements. The model assumes a decline in HRQL when patients progress from non-cirrhotic health states to compensated cirrhosis, DCC, HCC and liver transplant. However, an increase in HRQL is modelled when patients achieve SVR or receive a liver transplant.

The model incorporates costs associated with: treatment, monitoring, adverse events (including treatments, management, and outpatient, GP and specialist visits), and health state. Sofosbuvir/velpatasvir has a confidential Wales Patient Access Scheme in place. Comparator acquisition costs have been sourced from the British National Formulary[39]. Monitoring costs have been informed by the literature[35,37,40], and in some instances expert opinion; unit costs have been inflated to reflect NHS reference costs for 2014-2015[41]. The resource use associated with treatment-related adverse events reflects previous NICE submissions[19,35,36], the literature[42] and key opinion leader opinion. Unit costs for these have been taken from the British National Formulary[43], NHS reference costs[41], and PSSRU costs[44]. The resource use associated with health states is reflective of recent health technology appraisals, and has further been informed by the literature[35-37,45,46]. The costs for the most advanced stages of the disease are informed by an observational study on patients recruited from three hepatology centres in London, Newcastle and Southampton[37]. All health state costs have been updated to 2014/2015 costs using the Hospital and Community Health Services (HCHS) Pay and Prices Index[47].

In addition to those mentioned above, the model includes a number of noteworthy assumptions and simplifications, including:

- While patients with compensated cirrhosis who reach SVR are followed-up over a lifetime (follow-up costs are applied during that time), non-cirrhotic patients with SVR are only followed until the end of year two.
- It is assumed that achieving SVR is permanent and that transitioning back to non-SVR health states is not possible. This assumption was validated by external key opinion leaders and is consistent with other chronic hepatitis C economic models[14,35-37].
- The model assumes that no quality of life, or adverse event and cost implications persist once treatment is discontinued. Patients return to the quality of life utility value relevant to the post treatment health state they are in, and future adverse events and their associated costs cannot occur.

A range of one-way sensitivity and scenario analyses test the influence of the uncertainty in the parameters and structural assumptions on the robustness of the base case results. Sensitivity analyses explore the impact of varying: treatment costs, health states costs, utility values, transitional probabilities, discount rates, the probability of death for the general population; and treatment specific SVRs and adverse events. Scenario analyses additionally test the cost-effectiveness of sofosbuvir/velpatasvir against additional treatments which are less relevant and used less frequently in current practice in GT1 and GT4 patients. Probabilistic sensitivity analyses further quantify the parameter uncertainty in the model surrounding: SVR rates, utilities, health state costs, and transition probabilities.

4.1.2 Results

A selection of the results of the base case pair-wise comparisons is detailed in Table 6. Depending on the patient population and the choice of comparator, sofosbuvir/velpatasvir ranges from being the dominant treatment to having an incremental cost per QALY of £32,595. Some case point estimates also fall within the south-west quadrant of the cost effectiveness plane (that is, sofosbuvir/velpatasvir is shown to be less costly, but also less effective). For patients with GT4, pair-wise comparisons reveal how sofosbuvir/velpatasvir dominates, is of equal effectiveness but lower cost, or has an ICER ranging from £1,435 to £6,229 per QALY gained. For GT5 and GT 6 patients, sofosbuvir/velpatasvir dominates or ICERs range from £1,435 to £6,229 per QALY gained.

The company estimates that 49% and 46% of patients in Wales are of genotypes GT3 and GT1 respectively. The results for these sub-populations are generally favourable, as can be seen below. Notably, the base case results suggest that sofosbuvir/velpatasvir is a cost-effective treatment for GT3 treatment-naive patients without cirrhosis, and those who are interferon-ineligible.

Table 6. Results of the base case pair-wise comparisons of sofosbuvir/velpatasvir versus each comparator

Patient population		Comparator regimens	Total costs	Total QALYs	ICER (£/QALY)
Genotype 1a	treatment naive, non-cirrhotic	Epclusa®	£31,257	17.23	-
		BSC	£16,304	13.63	£4,154
		PR-48	£20,880	15.22	£5,157
		LS-8	£29,713	17.10	£11,647
		OPRDR-12	£39,101	17.20	Epclusa® dominates
		SoD-12	£62,383	17.32	£342,564 (SW)
		SoPR-12	£41,331	16.98	Epclusa® dominates
		SPR	£33,817	16.61	Epclusa® dominates
	treatment naive, cirrhotic	Epclusa®	£48,535	10.18	-
		BSC	£35,790	4.98	£2,448
		PR-48	£43,577	6.36	£1,298
		LS-12	£60,349	9.88	Epclusa® dominates
		OPRDR-24	£92,126	9.84	Epclusa® dominates
		SoPR-12	£61,014	9.16	Epclusa® dominates
		SPR	£55,825	8.16	Epclusa® dominates
	treatment experienced, non-cirrhotic	Epclusa®	£30,596	16.24	-
		BSC	£15,332	13.08	£4,830
		PR-48	£21,412	13.66	£3,562
		LS-12	£41,891	16.17	Epclusa® dominates
		OPRDR-12	£38,610	16.18	Epclusa® dominates
		SoD-12	£61,747	16.32	£390,941 (SW)
		SoPR-12	£43,169	15.45	Epclusa® dominates
		SPR	£38,537	15.59	Epclusa® dominates
	treatment experienced, cirrhotic	Epclusa®	£46,903	9.78	-
		BSC	£35,361	4.93	£2,380
		PR-48	£42,400	5.55	£1,065
		LS-12	£60,288	9.12	Epclusa® dominates
		OPRDR-24	£90,077	9.58	Epclusa® dominates

Patient population		Comparator regimens	Total costs	Total QALYs	ICER (£/QALY)
		SoPR-12	£60,643	8.50	Epclusa® dominates
		SPR	£57,519	8.60	Epclusa® dominates
Genotype 1b	treatment naive, non-cirrhotic	Epclusa®	£30,873	17.32	-
		BSC	£16,304	13.63	£3,948
		PR-48	£20,880	15.22	£4,752
		LS-8	£29,713	17.10	£5,193
		OPRD-12	£37,508	17.29	Epclusa® dominates
		SoD-12	£62,383	17.32	Equal effectiveness, but Epclusa® has lower cost
		SoPR-12	£41,331	16.98	Epclusa® dominates
		SPR	£33,817	16.61	Epclusa® dominates
	treatment naive, cirrhotic	Epclusa®	£49,252	9.97	-
		BSC	£35,790	4.98	£2,697
		PR-48	£43,577	6.36	£4,752
		LS-12	£60,349	9.88	Epclusa® dominates
		OPRDR-12	£56,300	10.17	£34,531 (SW)
		SoPR-12	£61,014	9.16	Epclusa® dominates
		SPR	£55,825	8.16	Epclusa® dominates
	treatment experienced, non-cirrhotic	Epclusa®	£30,237	16.32	-
		BSC	£15,332	13.08	£4,600
		PR-48	£21,412	13.66	£3,320
		LS-12	£41,891	16.17	Epclusa® dominates
		OPRD-12	£37,246	16.32	Equal effectiveness, but Epclusa® has lower cost
		SoD-12	£61,747	16.32	Equal effectiveness, but Epclusa® has lower cost
		SoPR-12	£43,169	15.45	Epclusa® dominates
		SPR	£38,537	15.59	Epclusa® dominates
	treatment experienced, cirrhotic	Epclusa®	£47,635	9.58	-
		BSC	£35,361	4.93	£2,639
		PR-48	£42,400	5.55	£1,299
		LS-12	£60,288	9.12	Epclusa® dominates
		OPRDR-12	£55,073	9.66	£87,498 SW
		SoPR-12	£60,643	8.50	Epclusa® dominates
		SPR	£57,519	8.60	Epclusa® dominates
Genotype 2	treatment naive, non-cirrhotic	Epclusa®	£30,886	17.29	-
		BSC	£14,676	14.17	£5,183
		PR-24	£10,157	16.66	£32,595
	treatment naive, cirrhotic	Epclusa®	£48,409	10.18	-
		BSC	£35,790	4.98	£2,424
		PR-24	£30,315	8.72	£12,384
	treatment experienced, non-cirrhotic	Epclusa®	£30,165	16.31	-
		BSC	£13,771	13.54	£5,929
		PR-48	£18,787	14.49	£6,266
		SoR-12	£40,760	15.78	Epclusa® dominates
	treatment experienced, cirrhotic	Epclusa®	£46,851	9.757	-
		BSC	£35,361	4.928	£2,379
		PR-48	£39,111	6.757	£2,580
		SoR-12	£55,005	9.762	£1,774,628 (SW)
Genotype 3	treatment naive, non-cirrhotic	Epclusa®	£31,276	17.24	-
		BSC	£18,686	12.83	£2,854
		PR-24	£12,318	16.00	£15,199
	treatment naive, cirrhotic	Epclusa®	£49,810	9.82	-
		BSC	£35,790	4.98	£2,892
		PR-24	£37,198	6.58	£3,893
		SoPR-12	£59,727	9.71	Epclusa® dominates
	treatment experienced, non-cirrhotic	Epclusa®	£31,791	15.98	-
		BSC	£17,647	12.37	£3,926
		PR-48	£21,235	13.77	£4,799
		SoPR-12	£40,525	16.06	£104,232 (SW)
	treatment experienced, cirrhotic	Epclusa®	£48,877	9.26	-
		BSC	£35,361	4.93	£3,120

Patient population		Comparator regimens	Total costs	Total QALYs	ICER (£/QALY)
		PR-48	£39,111	6.76	£3,904
		SoPR-12	£58,734	9.07	Epclusa® dominates
Genotype 2 IFNi	treatment naive, non-cirrhotic	Epclusa®	£30,886	17.29	-
		BSC	£14,676	14.17	£5,183
		SoR-12	£39,551	17.18	Epclusa® dominates
	treatment naive, cirrhotic	Epclusa®	£48,409	10.18	-
		BSC	£35,790	4.98	£2,424
		SoR-12	£57,784	9.83	Epclusa® dominates
	treatment experienced, non-cirrhotic	Epclusa®	£30,165	16.31	-
		BSC	£13,771	13.54	£5,929
		SoR-12	£40,760	15.78	Epclusa® dominates
	treatment experienced, cirrhotic	Epclusa®	£46,851	9.757	-
		BSC	£35,361	4.928	£2,379
		SoR-12	£55,005	9.762	Epclusa® dominates
Genotype 3 IFNi	treatment naive, non-cirrhotic	Epclusa®	£31,276	17.24	-
		BSC	£18,686	12.83	£2,854
		SoD-12	£66,141	16.34	Epclusa® dominates
	treatment naive, cirrhotic	Epclusa®	£49,810	9.82	-
		BSC	£35,790	4.98	£2,892
		SoDR-24	£88,194	8.00	Epclusa® dominates
		SoR-24	£97,229	8.85	Epclusa® dominates
	treatment experienced, non-cirrhotic	Epclusa®	£31,791	15.98	-
		BSC	£17,647	12.37	£3,926
		SoD12	£66,538	15.20	Epclusa® dominates
	treatment experienced, cirrhotic	Epclusa®	£48,877	9.26	-
		BSC	£35,361	4.93	£3,120
		SoDR-24	£84,651	8.29	Epclusa® dominates
		SoR-24	£98,396	7.79	Epclusa® dominates
DCC	treatment naive	Epclusa®R	£124,324	3.84	-
		LSR-12	£131,653	3.68	Epclusa®R dominates
	treatment experienced	Epclusa®R	£121,081	3.71	-
		LSR-12	£128,574	3.56	Epclusa®R dominates

BSC: best supportive care; DCC: decompensated cirrhosis; Epclusa®R: sofosbuvir/velpatasvir +ribavirin; ICER: incremental cost-effectiveness ratio; IFNi: interferon-ineligible; LS: ledipasvir/sofosbuvir; LSR: ledipasvir/sofosbuvir + ribavirin; OPRDR: ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin; OPRD: ombitasvir/paritaprevir/ritonavir + dasabuvir; OPRR: ombitasvir/paritaprevir/ritonavir + ribavirin; PR: peginterferon + ribavirin; QALY: quality-adjusted life-year; SoD: sofosbuvir + daclatasvir; SoPR: sofosbuvir + peginterferon + ribavirin; SPR: simeprevir + peginterferon + ribavirin; SoR: sofosbuvir + ribavirin

The results of the univariate analyses reveal how the base case findings are generally most sensitive to treatments costs, SVRs and discount rates; especially for treatment-naive patients. In some instances there are also sensitivities to changes in the utility values for patients who are not receiving treatment. Table 7 details some of the most noteworthy analyses and an exploration of their plausibility.

Table 7. Results of sensitivity analyses

Scenario/Parameter	ICER	Plausibility
GT3 TN NC - Epclusa® v PR-24: a) SVR of 0.96 for Epclusa®	a) £17,120	Given the lack of direct treatment comparison data and the inability to conduct an NMA, there is resultant uncertainty surrounding relative SVRs. a) The ASTRAL-3 study reveals an SVR rate in the GT3 TN NC population of 98% (n=160/163). However, the lower CI is 96%. This scenario therefore arguably offers a potentially plausible alternative to the base case.
GT1 TN NC - Epclusa® v LS-8: a) SVR of 0.98 for LS-8 b) SVR of 0.95 for Epclusa®	a) £128,146 b) £40,332	a) Given the similarity in costs and SVR rates between these treatments, this ICER is highly sensitive to relative SVR rates. Caution is therefore required when viewing these sensitivity analyses results. Real-world data supports an SVR rate of 95% (TRIO study). However, if a 95% CI is calculated using these data, the upper CI corresponds with the 98% SVR rate used in the sensitivity analyses. b) AWTTC calculated the confidence intervals for this patient sub-population. These additional calculations revealed that this ICER is unlikely to be considered a plausible alternative to the base case.
CI: confidence interval; GT: genotype; ICER: incremental cost-effectiveness ratio; LS-8: ledipasvir/sofosbuvir (for 8 weeks); NC: non-cirrhotic; NMA: network meta-analysis; PR: peginterferon + ribavirin; SVR: sustained virologic response; TN: treatment-naive		

The probabilistic sensitivity analyses reveal a high degree of uncertainty surrounding the base case estimates in some of the populations of interest (see Table 8). The subgroups with the highest amount of uncertainty being: GT4, GT3, GT1, GT1a and GT1b. Given that GT1 (which includes GT1a and GT1b) patients account for a large proportion of patients in Wales; these findings are of particular significance. GT3 patients are also a significant group for consideration. However, it should be noted that in contrast to the wider GT3 population, there is a particularly high probability of sofosbuvir/velpatasvir being cost effective for GT3INFi patients. Likewise, patients with GT5, GT6 and DCC are associated with a relatively high probability of sofosbuvir/velpatasvir being cost effective. For GT4 patients the probability of being cost effective at the £20,000 and £30,000 willingness-to-pay thresholds ranged between 51–58% and 52–56%, respectively. For GT5, these probability ranges are 97–91% and 88–95%, respectively. For GT6 patients, they range from 87–93% and 87–95%, respectively. It should be noted that the high degree of uncertainty reported somewhat reflects the heightened sensitivity to relative SVR rates in some of the comparisons conducted.

Table 8. Results of the probabilistic sensitivity analyses

Patient population		Probability of Epclusa® being a cost effective treatment at WTP thresholds of:	
		£20,000	£30,000
GT1a	Treatment naive / non-cirrhotic	29%	27%
	Treatment naive / cirrhotic	53%	47%
	Treatment experienced / non-cirrhotic	43%	36%
	Treatment experienced / cirrhotic	64%	57%
GT1b	Treatment naive / non-cirrhotic	31%	29%
	Treatment naive / cirrhotic	37%	33%
	Treatment experienced / non-cirrhotic	43%	38%
	Treatment experienced / cirrhotic	43%	39%
GT2	Treatment naive / non-cirrhotic	42%	54%
	Treatment naive / cirrhotic	61%	67%
	Treatment experienced / non-cirrhotic	87%	83%
	Treatment experienced / cirrhotic	64%	61%
GT3	Treatment naive / non-cirrhotic	59%	71%
	Treatment naive / cirrhotic	63%	59%
	Treatment experienced / non-cirrhotic	64%	57%
	Treatment experienced / cirrhotic	65%	63%
GT2INFi	Treatment naive / non-cirrhotic	72%	67%
	Treatment naive / cirrhotic	62%	59%
	Treatment experienced / non-cirrhotic	88%	84%
	Treatment experienced / cirrhotic	64%	61%
GT3INFi	Treatment naive / non-cirrhotic	98%	95%
	Treatment naive / cirrhotic	98%	94%
	Treatment experienced / non-cirrhotic	98%	95%
	Treatment experienced / cirrhotic	95%	89%
DCC	Treatment naive	78%	79%
	Treatment experienced	77%	78%

DCC: decompensated cirrhosis; GT: genotype; ICER: incremental cost effectiveness ratio; IFNi: interferon-ineligible; WTP: willingness to pay

The scenarios analyses revealed that all additional comparators considered were dominated by sofosbuvir/velpatasvir. Given these results and the fact that the additional comparators used for these scenarios are generally considered less applicable than those used in the base case analyses, they are not considered plausible alternatives to the base case.

4.1.3 AWTTC critique

The approach the company has taken to evaluate cost-effectiveness is characterised by both strengths and limitations, the most salient of which are detailed below.

Strengths:

- The submission gives a detailed, transparent account of most of the methods and data sources used in the analysis.
- Where possible, the company has used validated resource use data. Clinical expert opinion has also been sought to validate the major assumptions underlying the model.
- A variety of sensitivity analyses have been conducted to test the robustness of the model to parameter changes.

- The submission includes an extensive number of comparisons by patient population.

Limitations:
- The efficacy data used in the models is taken from trials that were not powered specifically for sub-population analysis. This creates uncertainty around the efficacy data used in the model. Furthermore, the lack of direct treatment comparison data, the inability to conduct an NMA, and the use of naive comparisons further compounds this uncertainty. While the company have approached data limitations in a reasonable manner, this does not negate these uncertainties.
- The transition probability between the non-cirrhotic and compensated cirrhosis health states for each genotype is informed by a large US study[29]. This study was chosen on the basis of it offering a patient sample size considerably larger than alternative studies and the most recent date of publication. While these study findings have been validated as being broadly relevant to the demographics of the UK chronic hepatitis C population by two English clinical experts, and the study selection rationale are reasonable, there remains some uncertainty surrounding these values.
- The use of SF–6D values instead of EQ–5D for on-treatment utilities deviates from standard AWMSG requisites, and is not in keeping with the other utility values in the model which are based on EQ–5D values. The company justify the use of the values, stating that there is currently no clear consensus regarding the most appropriate mapping algorithm. However, it would have been insightful for this to have been explored via scenario analyses.
- Patients receiving no treatment are monitored for six weeks, which is likely to be a conservative assumption (that is, underestimates associated costs).

4.2 Review of published evidence on cost-effectiveness
A literature review conducted by AWTTC did not identify any cost-effectiveness studies focused specifically on the treatment comparisons for the populations of interest included in this submission.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence
5.1.1 Context and methods
The company has used a prevalence of chronic HCV infection of 12,000 in Wales and assumed 971 of these patients will be treated in year one. The assumed genotype split of the treated cohort is GT1: 46%, GT2: 3%, GT3: 49%, GTs 4–6: 2%. The company considered current treatments for each of the genotype subgroups in order to estimate the total medicine acquisition costs of the treatments in a scenario without the introduction of sofosbuvir/velpatasvir. Medicine acquisition costs in a scenario in which sofosbuvir/velpatasvir displaces other treatments are calculated assuming displacement of existing medicines in each of the genotype subgroups. The estimated total uptake of sofosbuvir/velpatasvir in treated patients across all GTs was [commercial in confidence figure removed]. Net budget impact was obtained by subtracting the scenario without sofosbuvir/velpatasvir from the scenario with sofosbuvir/velpatasvir to obtain a [commercial in confidence text removed] budget impact [commercial in confidence text removed]. [commercial in confidence text removed]

5.1.2 Results
[Commercial in confidence text removed]

5.1.3 AWTTC critique

- The company has provided a concise estimate of budget impact based on net medicine acquisition cost following the introduction of sofosbuvir/velpatasvir.
- Only the first year of treatment has been considered; the evolution of budget impact over longer time periods is not known.
- The company has stated that long-term resource savings arising from avoiding more severe health states such as DCC, HCC and liver transplants may be achieved. In addition eradication of HCV would also lead to resource savings at longer time frames. These potential resource savings have not been included in the model. It is plausible that resources may be saved for patients where sofosbuvir/velpatasvir displaces a medicine with lower clinical efficacy.
- Net resource costs due to adverse events and monitoring have not been determined in the model. The company claims that since sofosbuvir/velpatasvir can be used across all GTs, the treatment reduces costs associated with HCV genotyping. However, the potential number of patients who would be treated without genotyping is not stated.

5.2 Comparative unit costs

Table 9. Examples of costs per course of treatment with sofosbuvir/velpatasvir and alternative chronic HCV treatment regimens (for patients without cirrhosis or with compensated cirrhosis)

Treatment regimen	Genotype	Example doses	Approximate regimen costs per patient[43,48]
Sofosbuvir/velpatasvir (Epclusa®)	All GTs	Sofosbuvir 400 mg OD, velpatasvir 100mg OD +/- ribavirin 1,000 mg/day for 12 weeks	£38,979 - £39,905
SoR-12	GT 2 and 3	Sofosbuvir 400 mg OD + ribavirin 1,000 mg/day for 12 weeks	£35,908
LS-12	GT 1,4	Ledipasvir 90mg OD, sofosbuvir 400mg OD for 12 weeks	£38,799
PR-24, PR-48	GTs 1-4	Peginterferon alfa-2a 180 micrograms /week + ribavirin 1,000 mg/day for 24 or 48 weeks	£4,838 or £9,676
Boceprevir + PR	GT1	Boceprevir 800 mg TID 24 or 44 weeks + PR 28 or 48 weeks	£22,475 or £40,474
Telaprevir + PR	GT1	Telaprevir 750 mg TID for 12 weeks + PR for 24 or 48 weeks	£27,476 or £32,313
SoPR-12, SoPR-24	GTs 1,3,6	Sofosbuvir 400 mg OD + PR for 12 or 24 weeks	£37,401 to £74,802
SPR	GT1,4	Simeprevir 150 mg OD for 12 weeks + PR for 24 or 48 weeks	£27,476 to £32,314
SoD-12, SoD-24	GT1,2,3 or 4	Daclatasvir 60 mg OD + sofosbuvir 400 mg OD for 12 or 24 weeks	£59,501 to £119,002
SoDR-24	GT3	Daclatasvir 60 mg OD + sofosbuvir 400 mg OD + ribavirin 1,000 mg/day for 24 weeks	£120,854
DPR	GT4	Daclatasvir 60 mg OD for 24 weeks + PR for 24 or 48 weeks	£53,871 to £58,707
OPRDR-12, OPRDR-24	GT1	Ombitasvir/paritaprevir/ritonavir 12.5mg/75mg/50mg BD + dasabuvir 250mg BD + ribavirin 1000 mg OD for 12 or 24 weeks	£35,926 or £71,852
OPRR-12, OPRR-24	GT4	ombitasvir/paritaprevir/ritonavir 12.5mg/75mg/50mg BD + ribavirin 1000 mg OD for 12 or 24 weeks	£33,126 or £66,252
BD: twice daily; GT: genotype; OD: once daily; TID: three times daily			

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, sofosbuvir/velpatasvir (Epclusa®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that sofosbuvir/velpatasvir (Epclusa®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

Several clinical trials of sofosbuvir/velpatasvir are ongoing, including:

- ASTRAL–5, a phase III open-label study to investigate the efficacy and safety of sofosbuvir/velpatasvir fixed dose combination for 12 weeks in adults with chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV)-1 co-infection[49].

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 July 2016
Date range of evidence search: No date limits were applied to database searches.

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Appendix 1: NICE guidance on hepatitis C treatment[12-16,18-20]

	Genotype 1a/1b			
	Treatment naive adults		Treatment experienced adults	
Treatment	**Without cirrhosis**	**With cirrhosis**	**Without cirrhosis**	**With cirrhosis**
Peginterferon alfa-2a with or without ribavirin[†]	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*
Peginterferon alfa-2b with or without ribavirin[§]	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*
Telaprevir plus peginterferon alfa plus ribavirin	12 weeks (ribavirin and peginterferon alfa for 24 or 48 weeks*)	12 weeks (ribavirin and peginterferon alfa for 48 weeks)	12 weeks (ribavirin and peginterferon alfa for 24 or 48 weeks*)	12 weeks (ribavirin and peginterferon alfa for 48 weeks)
Boceprevir plus peginterferon alfa plus ribavirin	28 or 48 weeks*	48 weeks	48 weeks	48 weeks
Simeprevir plus peginterferon alfa plus ribavirin	12 weeks (ribavirin and peginterferon alfa for 24 weeks)	12 weeks (ribavirin and peginterferon alfa for 24-48 weeks)	12 weeks (ribavirin and peginterferon alfa for 48 weeks)	12 weeks (ribavirin and peginterferon alfa for 48 weeks)
Ledipasvir/sofosbuvir	8 weeks	12 weeks	12 weeks	12 weeks[¶]
Sofosbuvir plus peginterferon alfa plus ribavirin	12 or 24 weeks	12 or 24 weeks	12 or 24 weeks	12 or 24 weeks
Daclatasvir plus sofosbuvir	12 weeks**	NR	12 weeks**	NR
Daclatasvir plus sofosbuvir with or without ribavirin	-	24 weeks[††]	-	24 weeks[††]
Ombitasvir/paritaprevir/ritonavir plus dasabuvir plus ribavirin	12 weeks (1a)	24 weeks (1a)	12 weeks (1a)	24 weeks (1a)
Ombitasvir/paritaprevir/ritonavir plus dasabuvir	12 weeks (1b)	NR	12 weeks (1b)	NR
	Genotype 2			
	Treatment naive adults		**Treatment experienced adults**	
Treatment	**Without cirrhosis**	**With cirrhosis**	**Without cirrhosis**	**With cirrhosis**
Peginterferon alfa-2a plus ribavirin[†]	16 or 24 weeks	16 or 24 weeks	16 or 24 weeks	16 or 24 weeks
Peginterferon alfa-2b with or without ribavirin[†]	24-48 weeks	24-48 weeks	24-48 weeks	24-48 weeks[§§§]
Sofosbuvir plus ribavirin	12 or 24 weeks[††]	12 or 24 weeks[††]	12 or 24 weeks	12 or 24 weeks
	Genotype 3			
	Treatment naive adults		**Treatment experienced adults**	
Treatment	**Without cirrhosis**	**With cirrhosis**	**Without cirrhosis**	**With cirrhosis**
Peginterferon alfa-2a plus ribavirin[†]	16 or 24 weeks	16 or 24 weeks	16 or 24 weeks	16 or 24 weeks
Peginterferon alfa-2b with or without ribavirin[†]	24-48 weeks	24-48 weeks	24-48 weeks	24-48 weeks
Sofosbuvir plus peginterferon alfa plus ribavirin	NR	12 or 24 weeks	12 or 24 weeks	12 or 24 weeks
Sofosbuvir plus ribavirin	NR	24 weeks[††]	NR	24 weeks[††]
Daclatasvir plus sofosbuvir	12 weeks**	NR	12 weeks**	NR
Daclatasvir plus sofosbuvir plus ribavirin	NR	24 weeks[††]	NR	24 weeks[††]

	Genotype 4			
	Treatment naive adults		Treatment experienced adults	
Treatment	**Without cirrhosis**	**With cirrhosis**	**Without cirrhosis**	**With cirrhosis**
Peginterferon alfa-2a plus ribavirin[†]	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*
Peginterferon alfa-2b with or without ribavirin[†]	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*	24 or 48 weeks*
Simeprevir plus peginterferon alfa plus ribavirin	12 weeks simeprevir (ribavirin and peginterferon alfa for 24 weeks)	12 weeks simeprevir (ribavirin and peginterferon alfa for 24-48 weeks) [†††]	12 weeks simeprevir (ribavirin and peginterferon alfa for 48 weeks)	12 weeks simeprevir (ribavirin and peginterferon alfa for 48 weeks)
Ledipasvir/sofosbuvir	NR	12 weeks	12 weeks	12 weeks[¶]
Sofosbuvir plus peginterferon alfa plus ribavirin	NR	12 or 24 weeks	NR	12 or 24 weeks
Daclatasvir plus sofosbuvir	12 weeks**[††]	NR	12 weeks**	NR
Daclatasvir plus sofosbuvir, with or without ribavirin	-	24 weeks[††]	-	24 weeks[††]
Daclatasvir plus peginterferon alfa plus ribavirin	24 weeks***	24 weeks	24 weeks***	24 weeks
Ombitasvir/paritaprevir/ritonavir plus ribavirin	12 weeks	24 weeks	12 weeks	24 weeks
	Genotypes 5 and 6			
	Treatment naive adults		**Treatment experienced adults**	
Treatment	**Without cirrhosis**	**With cirrhosis**	**Without cirrhosis**	**With cirrhosis**
Peginterferon alfa-2a plus ribavirin[†]	48 weeks	48 weeks	48 weeks	48 weeks
Peginterferon alfa-2b with or without ribavirin[†]	Not specified	Not specified	Not specified	Not specified
Sofosbuvir plus peginterferon alfa plus ribavirin	NR	12 or 24 weeks	NR	12 or 24 weeks

*Dependent on viral load and response to treatment
[†] Recommended monotherapy duration is 48 weeks; recommended ribavirin dose is 800–1200 mg/day dependent on body weight
[§] Recommended ribavirin dose is 800–1400 mg/day dependent on body weight
[¶] Recommended only if the following criteria are met: Child-Pugh class A; platelet count of ≥75,000/mm^3; no features of portal hypertension; no history of an HCV-associated decompensation episode; no previous treatment with an NS5A inhibitor
** Only for people with significant fibrosis
[††] Recommended only if the person cannot have interferon
[§§] Recommended treatment is 24 weeks for genotype 1a
*** Only for people with significant fibrosis or cirrhosis
[†††] With or without HIV infection
[§§§] 48 weeks in HIV infection

HCV: hepatitis C virus; NR: not recommended