AWMSG Secretariat Assessment Report
Glecaprevir/pibrentasvir (Maviret®▼) 100 mg/40 mg film-coated tablets

This assessment report is based on evidence submitted by AbbVie Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Glecaprevir/pibrentasvir (Maviret®▼) is indicated 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.
Dosing	The recommended dose of glecaprevir/pibrentasvir (Maviret®) is three tablets, taken orally, once daily with food. Recommended treatment durations are: • 8 weeks (no cirrhosis) or 12 weeks (with cirrhosis) for all treatment naive patients (any genotype); • 8 weeks (no cirrhosis) or 12 weeks (with cirrhosis) for genotype (GT)1,2, 4–6 HCV-infected patients who have failed prior therapy; • 16 weeks for all GT3 HCV-infected patients who have failed prior therapy. Refer to the Summary of Product Characteristics (SPC) for further details[2].
Marketing authorisation date	26 July 2017

2.0 DECISION CONTEXT

2.1 Background

Hepatitis C virus (HCV) is a blood-borne virus that causes liver inflammation, affects liver function and is one of the main causes of chronic liver disease[3,4]. Around 20% of people infected with HCV naturally clear the infection within six months, but most will develop chronic hepatitis C, which may be life-long[5]. Severe scarring of the liver (cirrhosis) develops in around 30% of infected people[4]. It is estimated that the mean time to development of cirrhosis is 20 years; although only 10–20% of people develop cirrhosis within this time[6]. In compensated cirrhosis the liver is still able to function. Without treatment, compensated cirrhosis can progress to decompensated cirrhosis, when the remaining liver is unable to compensate for the loss of function[7].

The aim of treatment is to cure the HCV infection[3]. Sustained virological response (SVR) is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after the end of treatment. The infection is cured in more than 99% of people who achieve an SVR. For people without cirrhosis, SVR is also generally associated with resolution of liver disease, although those with cirrhosis remain at risk of life-threatening complications[3].

Many HCV-infected people are asymptomatic and unaware of their infection, and therefore prevalence is difficult to establish[4]. In Wales, 480 laboratory reports of HCV infection were

recorded in 2012, mostly in males aged 25–49 years[8]. Estimates suggest that between 12,000 and 14,000 people in Wales have chronic HCV infection[9].

There are six main genotypes of HCV (GT1–6) and each genotype responds differently to treatment[4]. HCV genotype as well as previous treatment (if any) and cirrhosis status determines the choice of treatment regimen. A 2015 report estimated that in the UK, over 90% of chronic HCV infections are caused by HCV GT1 or GT3[8].

Glecaprevir/pibrentasvir (Maviret®) is a once-daily oral combination of two direct-acting antivirals: 100 mg glecaprevir and 40 mg pibrentasvir[1]. Glecaprevir and pibrentasvir respectively inhibit the HCV NS3/4A serine protease complex and HCV protein NS5A; both are essential for HCV viral replication[10].

2.2 Comparators

The comparators included in the company submission are:

- elbasvir/grazoprevir (Zepatier®) (GT1 and GT4)
- sofosbuvir/velpatasvir (Epclusa®) (GT1–6)
- ombitasvir/paritaprevir/ritonavir (Viekirax®) plus dasabuvir (Exviera®) with or without ribavirin (GT1)
- sofosbuvir/ledipasvir (Harvoni®) (GT1 and GT4)
- sofosbuvir (Sovaldi®) plus daclatasvir (Daklinza®) with or without ribavirin (as a scenario analysis only; GT3)
- ombitasvir/paritaprevir/ritonavir (Viekirax®) plus ribavirin (GT4)

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE) Technology Appraisal (TA) 430 (2017). Sofosbuvir–velpatasvir for treating chronic hepatitis C[4]
- NICE TA413 (2016). Elbasvir–grazoprevir for treating chronic hepatitis C[11]
- World Health Organization (2016). Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection[12]
- NICE TA365 (2015). Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C[13]
- NICE TA364 (2015). Daclatasvir for treating chronic hepatitis C[14]
- NICE TA363 (2015). Ledipasvir–sofosbuvir for treating chronic hepatitis C[15]
- NICE TA330 (2015). Sofosbuvir for treating chronic hepatitis C[16]
- European Association for the Study of the Liver (EASL) clinical practice guidelines (2015). Recommendations on treatment of hepatitis C[3]

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of ledipasvir/sofosbuvir (Harvoni®)[17], daclatasvir (Daklinza®)[18] and sofosbuvir/velpatasvir (Epclusa®)[19].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission presents data from 13 trials assessing the clinical effectiveness of glecaprevir/pibrentasvir, providing evidence across genotypes 1 to 6, and, within each genotype, for non-cirrhotic and compensated cirrhosis patients who were either treatment naïve or treatment experienced. In some trials, different treatment arms received different (and in some cases, unlicensed) doses of glecaprevir/pibrentasvir: this report focuses on evidence from patients using the licensed dose of glecaprevir 300 mg/pibrentasvir 120 mg once daily.

The following section briefly summarises efficacy results from the individual trials, followed by a summary of pooled safety results. The majority of trials were non-comparative/single arm (in some cases different doses and treatment durations of glecaprevir/pibrentasvir were compared). One trial (ENDURANCE-3) compared glecaprevir/pibrentasvir to sofosbuvir plus daclatasvir and one trial (ENDURANCE-2) compared glecaprevir/pibrentasvir to placebo; in all other trials patients only received glecaprevir/pibrentasvir. The company explored the possibility of using indirect comparison to estimate the clinical effectiveness of glecaprevir/pibrentasvir versus comparator treatments, but concluded that this was not feasible (see Section 3.3 for further discussion). Comparative clinical effectiveness evidence therefore relies on unadjusted comparison of outcomes with glecaprevir/pibrentasvir and comparator treatments using data from existing, separate trials of the comparators. Appendix Table 1 summarises the outcomes from this comparison according to genotype, prior treatment status and cirrhosis status.

3.1 Evidence on the efficacy of glecaprevir/pibrentasvir

Table 1 summarises the genotype, treatment status and cirrhosis status of patients in each trial. In all the trials, patients were at least 18 years of age with positive anti-HCV antibodies and plasma HCV RNA viral load ≥ 1,000 units/ml at the time of screening. Patients were excluded if they were co-infected with more than one HCV genotype, had a cause of liver disease other than chronic hepatitis C and a Child-Pugh score B or C, or a history of liver decompensation. Patients with compensated cirrhosis had a histological diagnosis of cirrhosis on liver biopsy and/or a FibroTest result indicative of cirrhosis. Any trial-specific patient characteristics are noted in Sections 3.1.1 to 3.1.12.

Across all trials the primary outcome was SVR12, defined as HCV RNA less than the lower limit of quantification at 12 weeks after the end of treatment. SVR12 outcomes for each trial are listed in Table 1. Secondary outcomes included on-treatment virologic failure and post-treatment relapse (12 weeks after end of treatment). In all trials patients were followed up for 24 weeks after treatment[1].

Table 1. Trial design and results

Trial	Patient eligibility criteria/characteristics			Treatment and duration[a]	Number of patients	SVR12, % (95% CI)
	Genotype	Treatment status	Cirrhosis status			
ENDURANCE-1	GT1	TN or TE-PRS	NC	G/P 8 weeks	351	99.1 (97.4, 99.7)
				G/P 12 weeks	352	99.7 (98.4, 99.9)
ENDURANCE-2	GT2	TN or TE-PRS	NC	G/P 12 weeks	202	99.5% (98.5, 100)
ENDURANCE-3	GT3	TN	NC	G/P 8 weeks	157	94.9 (91.5, 98.3)
				G/P 12 weeks	233	95.3 (92.6, 98.0)
				SOF + DCV 12 weeks	115	96.5 (93.2, 99.9)
ENDURANCE-4	GT4–6	TN or TE-PRS	NC	G/P 12 weeks	121	99.2 (97.6, 100.0)
SURVEYOR-I, Part 2	GT4–6	TN or TE-PR	NC	G/P 12 weeks	34	100.0 (89.8, 100)
	GT1			G/P 8 weeks	34	97.1 (85.1, 99.5)
SURVEYOR-II, Part 1	GT2	TN and TE-PR	NC	G/P 12 weeks	25	96.0 (80.5, 99.3)
	GT3			G/P 12 weeks	30	93.3 (78.7, 98.2)
SURVEYOR-II, Part 2	GT2	TN and TE-PR	NC	G/P 8 weeks	54	98.1 (90.2, 99.7)
	GT3	TN	NC	G/P 8 weeks	29	96.6 (82.8, 99.4)
	GT3	TE-PR	NC	G/P 12 weeks	24	¶¶
	GT3	TN	CC	G/P 12 weeks ± RBV	24	100.0 (86.2, 100)
SURVEYOR-II, Part 3	GT3	TE-PRS	NC	G/P 12 weeks	22	90.9 (72.2, 97.5)
	GT3	TE-PRS	NC	G/P 16 weeks	22	95.5 (78.2, 99.2)
	GT3	TN	CC	G/P 12 weeks	40	97.5 (87.1, 99.6)
	GT3	TE-PRS	CC	G/P 16 weeks	47	95.7 (85.8, 98.8)
SURVEYOR-II, Part 4	GT2	TN or TE-PRS	NC	G/P 8 weeks	145	97.9 (94.1, 99.3)
	GT4–6	TN or TE-PRS	NC	G/P 8 weeks	58	93.1 (83.6, 97.3)
EXPEDITION-1	GT1–2, GT4–6	TN or TE-PRS	CC	G/P 12 weeks	146	¶¶
EXPEDITION-4	GT1– 6	TN or TE-PRS (GT3 only)	NC or CC	G/P 12 weeks	104	98.1 (95.4, 100.0)
MAGELLAN-1, Part 1	GT1	TE-DAA	NC	G/P 12 weeks ± RBV	22	86.4 (66.7, 95.3)
MAGELLAN-1, Part 2	GT1, GT4–6[2]	TE-DAA	NC or CC	G/P 12 weeks	44	¶¶
				G/P 16 weeks	47	¶¶

[a]Results exclude patients receiving unlicensed doses of G/P. [2]Although GT1 and GT4–6 patients were eligible, results are not reported for any GT5 or GT6 patients, and only for 4 GT4 patients.
¶¶: commericial in confidence data removed
Abbreviations: CC: compensated cirrhosis; CI: confidence interval; DAA: direct-acting antiviral; DCV: daclatasvir; G/P: glecaprevir/pibrentasvir; GT: genotype; HCV: hepatitis C virus; NC: non-cirrhotic; RBV: ribavirin; SOF: sofosbuvir; SVR12: sustained virologic response 12 weeks post-treatment; TE-DAA: treatment experienced with anti-HCV DAA-containing regimen; TE-PR: treatment-experienced with regimens containing peginterferon and/or ribavirin; TE-PRS: treatment-experienced with regimens containing interferon; TN: treatment-naïve.

3.1.1 ENDURANCE-1

ENDURANCE-1 enrolled GT1-infected non-cirrhotic patients, with or without HIV co-infection, who were treatment-naïve or treatment-experienced[1]. Patients received 12 or 8 weeks of glecaprevir/pibrentasvir treatment. The company submission focuses on intent-to-treat (ITT) results from direct-acting antiviral-naïve patients who did not have HIV co-infection (the ITT-PS population): SVR12 rates were 99.1% (95% confidence interval [CI]: 98.1% to 100%) and 99.7% (95% CI: 99.1% to 100%) in patients treated for 12 and 8 weeks respectively. SVR12 rates in the ITT population were similar to the ITT-PS population (99.1% for the 8-week regimen and 99.7% for the 12 week regimen).

In the 8-week treatment arm, one patient experienced on-treatment virologic failure; three non-responders across both treatment arms failed to achieve SVR12 for non-virologic reasons. No significant association was detected between SVR12 and any subgroup tested. [Commercial in confidence text removed].

3.1.2 ENDURANCE-2

ENDURANCE-2 enrolled GT2-infected non-cirrhotic patients who were treatment-naïve or treatment-experienced with interferon, peginterferon, ribavirin, and/or sofosbuvir[1]. All patients (n = 202) received 12 weeks of glecaprevir/pibrentasvir. Results are presented for the ITT population, excluding patients who had previously failed treatment with sofosbuvir in combination with ribavirin, with or without peginterferon (n = 196). In this group, SVR12 rates were 99.5% (95% CI: 98.5 to 100.0). All patients in whom prior treatment with sofosbuvir plus ribavirin (with or without peginterferon) had failed achieved SVR12. One patient was considered a non-responder due to missing SVR12 data. No significant association was detected between SVR12 and any of the subgroup variables tested[1].

3.1.3 ENDURANCE-3

ENDURANCE-3 enrolled GT3-infected non-cirrhotic patients who were treatment-naïve[1]. Patients were treated with glecaprevir/pibrentasvir for 8 or 12 weeks, or sofosbuvir plus daclatasvir 400 mg/60 mg for 12 weeks; SVR12 rates were 94.9%, 95.3% and 96.5%, respectively. Differences between the three treatment arms were not statistically significant, and 12-week treatment with glecaprevir/pibrentasvir was demonstrated to be noninferior to sofosbuvir plus daclatasvir according to prespecified criteria.[Commercial in confidence text removed].

3.1.4 ENDURANCE-4

ENDURANCE-4 enrolled non-cirrhotic patients with GT4, GT5 or GT6 infection who were treatment-naïve or treatment-experienced with interferon, peginterferon, ribavirin and/or sofosbuvir[1]. All patients received treatment with glecaprevir/pibrentasvir for 12 weeks. In the ITT population, the SVR12 rate was 99.2%; no patients experienced on-treatment virologic failure or post-treatment relapse. SVR12 rates were similar across each genotype subgroup. [Commercial in confidence text removed].

3.1.5 SURVEYOR-I, Part 2

SURVEYOR-I, Part 2 included GT1-, GT4-, GT5- or GT6-infected patients who were non-cirrhotic and treatment-naïve or treatment-experienced with peginterferon and/or ribavirin[1]. GT1-infected patients were treated with glecaprevir/pibrentasvir for 8 weeks; other genotypes were treated for 12 weeks. In the ITT GT1 population, SVR12 was 97.1%. Among the ITT GT4, GT5 and GT6 population SVR12 was 100%. No patients experienced virologic failure[1].

3.1.6 SURVEYOR-II, Parts 1 and 2

SURVEYOR-II, Part 1 included GT2- or GT3- infected non-cirrhotic patients who were treatment-naïve or treatment-experienced with peginterferon and/or ribavirin; all patients were treated with 12 weeks of glecaprevir/pibrentasvir[1]. SURVEYOR-II, Part 2 included GT2- or GT3-infected non-cirrhotic patients who were treatment-naïve or

treatment-experienced with peginterferon and/or ribavirin; patients were treated with glecaprevir/pibrentasvir for 8 weeks. The SVR12 rates in the ITT GT2 population following 12 weeks and 8 weeks of glecaprevir/pibrentasvir treatment were 96.0% and 98.1% respectively. The SVR12 rate in the ITT G3 population following 12 weeks glecaprevir/pibrentasvir treatment was 93.3%. No patients in GT2 population experienced virologic failure. Treatment-naïve GT3 patients with compensated cirrhosis were treated with glecaprevir/pibrentasvir, with or without ribavirin (800 mg), for 12 weeks. The SVR12 rate in this population was 100% with no patients experiencing virologic failure[1]. [Commercial in confidence text removed].

3.1.7 SURVEYOR-II, Part 3

SURVEYOR-II, Part 3, enrolled GT3-infected cirrhotic or non-cirrhotic patients who were treatment-naive or treatment-experienced with interferon, peginterferon, ribavirin, and/or sofosbuvir. Non-cirrhotic patients who were treatment-experienced were randomised to receive treatment with glecaprevir/pibrentasvir for 12 or 16 weeks[1]. In this group, the SVR12 rates after 12 and 16 weeks of glecaprevir/pibrentasvir treatment were 90.9% and 95.5% respectively. Across both treatment durations there were three virologic failures due to relapse[1].

Patients with compensated cirrhosis who were treatment-naïve received glecaprevir/pibrentasvir for 12 weeks; GT3 patients with compensated cirrhosis who were treatment-experienced with interferon, peginterferon, ribavirin, and/or sofosbuvir received glecaprevir/pibrentasvir for 16 weeks[1]. In the ITT treatment-naïve population the SVR12 rate was 97.5%; in the ITT treatment-experienced population the SVR12 rate after 16 weeks glecaprevir/pibrentasvir treatment was 95.7%. No treatment-naïve patients experienced virologic failure; in the treatment-experienced group there were two virologic failures (one on-treatment virologic failure and one due to relapse)[1].

3.1.8 SURVEYOR-II, Part 4

SURVEYOR-II, Part 4 enrolled GT2-, GT4-, GT5- or GT6-infected patients who were non-cirrhotic and treatment-naïve or treatment-experienced with interferon, peginterferon, ribavirin and/or sofosbuvir[1]. All patients received treatment with glecaprevir/pibrentasvir for 8 weeks. SVR12 rates were 96.6% (95% CI: 94.1 to 99.3) in the ITT population, 97.9% in the ITT GT2 population and 93.1% in the ITT GT4, GT5 and GT6 population. Two GT2-infected patients relapsed within 12 weeks after completion of treatment[1].

3.1.9 EXPEDITION-1

In EXPEDITION-1, compensated cirrhosis patients with GT1, GT2, GT4, GT5 or GT6 infection who were treatment-naïve or treatment-experienced with interferon, peginterferon, ribavirin, and/or sofosbuvir received 12 weeks of glecaprevir/pibrentasvir treatment[1]. SVR12 was achieved by 99.3% of the ITT patient population; one patient experienced post-treatment relapse[1].

3.1.10 EXPEDITION-4

EXPEDITION-4 enrolled patients with renal impairment (chronic kidney disease Stage 4/5) who were non-cirrhotic or had compensated cirrhosis with GT1, GT2, GT3, GT4, GT5 or GT6 infection. GT3 patients were treatment-naïve; patients infected with GT1, GT2, GT4, GT5 or GT6 infection were treatment-naïve or treatment-experienced with interferon, peginterferon, ribavirin, and/or sofosbuvir. All patients were treated with glecaprevir/pibrentasvir for 12 weeks[1]. In the ITT population SVR12 rate was 98.1% and no patients experienced virologic failure[1].

3.1.11 MAGELLAN-1, Part 1

GT1 infected non-cirrhotic patients who had failed a prior anti-HCV direct-acting antiviral-containing regimen were treated for 12 weeks with glecaprevir/pibrentasvir[1]. In

the ITT population the SVR12 rate was 86.4%; on-treatment virologic failure occurred in one patient[1].

3.1.12 MAGELLAN-1, Part 2

In MAGELLAN-1, Part 2, patients with GT1, GT4, GT5 or GT6 infection who were non-cirrhotic or had compensated cirrhosis and had failed a prior anti-HCV direct-acting antiviral-containing regimen were treated with glecaprevir/pibrentasvir for 12 or 16 weeks[1]. SVR rates 12 weeks after 12 or 16 week glecaprevir/pibrentasvir treatment were 88.6% and 91.5% respectively. In the 12 week treatment group there was one on-treatment virologic failure and three post-treatment relapses. In the group treated with glecaprevir/pibrentasvir for 16 weeks, 4 patients experienced on-treatment virologic failure[1].

3.2 Comparative safety

Data from the ENDURANCE-2 and ENDURANCE-3 studies demonstrated a similar safety profile for glecaprevir/pibrentasvir 300 mg/120 mg once daily compared with placebo and sofosbuvir plus daclatasvir (400 mg and 60 mg once daily, respectively)[1]. The company submission also included an integrated safety summary combining data from eight phase II and III registrational studies with data from the treatment arms of three supportive phase II studies which used glecaprevir/pibrentasvir 300 mg/120 mg once daily. The largely non-comparative integrated safety summary comprised treatment-naive and treatment-experienced GT1-6 HCV infected patients with compensated liver disease (with and without cirrhosis). In the integrated safety analysis (n = 2,265; excludes patients with chronic kidney disease stage 4/5) the most common study drug-related adverse events (ADRs) (occurring in ≥10% of patients) were headache and fatigue. ADRs were mostly mild in severity; serious ADRs and ADRs that lead to premature study drug discontinuation were rare (≤ 0.1%).

In patients with chronic kidney disease stage 4/5 (n = 104; includes patients on dialysis), the most common ADRs were pruritus, fatigue and nausea. Two patients discontinued the study drug prematurely due to ADRs. ADRs were mostly mild or moderate in severity and there were no serious ADRs.

Overall, no specific safety concerns were identified with the use of glecaprevir/pibrentasvir 300 mg/120 mg once daily[1].

3.3 AWTTC critique

- Glecaprevir/pibrentasvir is a once-daily, interferon- and ribavirin-free oral HCV treatment that can be used in a wide spectrum of patients infected with HCV: it can be used in genotypes 1–6, in patients who are treatment naive or experienced, with or without cirrhosis. Glecaprevir/pibrentasvir can also be used in HCV-infected genotype 2, 3, 5 and 6 patients with severe renal impairment (including those on dialysis), who have no other licensed treatment options. However, it should be noted that the company submission does not cover the use of glecaprevir/pibrentasvir in HCV-infected patients with decompensated cirrhosis.
- The submission includes evidence on the effectiveness of glecaprevir/pibrentasvir across 24 subgroups: 6 HCV genotypes, in patients without cirrhosis or with compensated cirrhosis, and in both treatment-naïve and treatment-experienced patient subgroups. Across these subgroups, estimated SVR12 rates range from 87.5% to 100%. GT1 and GT3 are the most common types of HCV infection in the UK. In studies of GT1 patients, SVR12 after glecaprevir/pibrentasvir treatment ranged from 95.7% to 100%, depending on prior treatment and cirrhosis status. In studies of GT3 patients, SVR12 after glecaprevir/pibrentasvir treatment was 94.1% to 98.4%.
- The glecaprevir/pibrentasvir SPC does not recommend its use in treatment-experienced patients with prior exposure to NS3/4A- and/or

NS5A-inhibitors[2]. In most of the clinical trials, treatment-experienced patients had received prior treatment with regimens containing interferon, peginterferon, ribavirin, and/or sofosbuvir. Evidence on the use of glecaprevir/pibrentasvir in patients who had previously received a direct-acting antiviral-containing regimen is limited (113 patients were studied in two trials, MAGELLAN-1, Part 1 and MAGELLAN-1, Part 2).

- The company have based their choice of comparators on treatments for HCV approved by AWMSG and NICE, along with feedback from Welsh clinicians. Glecaprevir/pibrentasvir is only compared to newer direct-acting antiviral therapies, and is not compared to any interferon-based treatment regimens. This approach is in line with EASL guidelines, which recommend interferon-free regimens as the best treatment options for HCV-infected patients without cirrhosis or with compensated cirrhosis[3]. Genotype-specific choices of comparator are broadly aligned with EASL guidelines[3], recent or ongoing AWMSG[19] and NICE[20,21] appraisals of HCV treatments, and independent clinical advice sought by AWTTC.
- Evidence submitted on the clinical effectiveness of glecaprevir/pibrentasvir is largely drawn from single-arm, non-comparative trials. Evidence directly comparing glecaprevir/pibrentasvir to any active comparator is limited to a single trial (ENDURANCE-3), and evidence searches conducted by AWTTC have not identified any additional studies of the effectiveness of glecaprevir/pibrentasvir versus any active comparator. The company has conducted a systematic review on the use of glecaprevir/pibrentasvir and comparator treatments to explore the possibility of using indirect comparison to estimate the clinical effectiveness of glecaprevir/pibrentasvir versus comparator treatments. However, this review found that the majority of trials conducted with comparator treatments also used a non-comparative design. It is therefore not feasible to form a network between glecaprevir/pibrentasvir and any relevant comparator therapies, and comparative clinical effectiveness evidence relies on unadjusted comparison of glecaprevir/pibrentasvir to the comparators using outcomes from single-arm trials of each treatment (summarised in Appendix Table 1). Such a comparison does not take into account any differences in patient characteristics or trial design that might affect outcomes, and is therefore liable to uncertainty. Nevertheless, given the difficulties in comparing evidence from HCV trials, this approach has been used in health technology assessments of other HCV treatments that are recommended for use by AWMSG[19] and NICE[4].
- Compared with other available direct-acting antivirals, glecaprevir/pibrentasvir offers a shorter duration of treatment (8 weeks) across genotypes 2–6 in non-cirrhotic treatment-naive patients, and across genotypes 1, 2 and 4–6 in non-cirrhotic treatment-experienced patients.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes cost utility analyses (CUA) comparing glecaprevir/pibrentasvir 300 mg/120 mg, oral once daily, for the treatment of adults with chronic HCV infection. Patient groups are defined by HCV genotype, treatment history and fibrosis status; resulting in 24 subgroups for separate economic analysis to determine cost-effectiveness (see Table 3). As discussed in Section 2.2, comparators vary according to genotype; these are listed in Table 2.

Table 2: Comparators to glecaprevir/pibrentasvir according to genotype

Comparator	GT1	GT2	GT3	GT4	GT5	GT6
OBV/PTV/RTV + DSV ± RBV	X					
OBV/PTV/RTV ± RBV				X		
SOF/VEL	X	X	X	X	X	X
EBR/GZR ± RBV	X			X		
SOF/LDV ± RBV	X			X		
(SOF + DCV ± RBV)[a]			(X)			

Abbreviations: DCV: daclatasvir; DSV: dasabuvir; EBR/GZR: elbasvir/grazoprevir; OBV/PTV/RTV: ombitasvir/paritaprevir/ritonavir; RBV: ribavirin; SOF/LDV: sofosbuvir/ledipasvir; SOF/VEL: sofosbuvir/velpatasvir.

[a]Scenario analysis only, on the basis of company-sought clinical expert opinion that this combination is only administered to GT3 treatment-experienced patients in rare circumstances.

Table 3: Model populations and genotypes

Genotype	Treatment naive No cirrhosis	Treatment experienced No cirrhosis	Treatment naive Compensated cirrhosis	Treatment experienced Compensated cirrhosis
1	X	X	X	X
2	X	X	X	X
3	X	X	X	X
4	X	X	X	X
5	X	X	X	X
6	X	X	X	X

Each CUA takes the form of a cohort Markov model, comprising yearly cycles with two key phases: a treatment phase and a post-treatment natural disease progression phase. The model adopts a lifetime time horizon (70 years after starting age) and a NHS Wales/Personal Social Services perspective. The model assumes that patients do not experience disease progression or die during the treatment phase (year one). With successful treatment patients achieve SVR, which is assumed to be permanent with no spontaneous reactivation of disease. Those who do not achieve SVR progress to more severe health states, namely decompensated cirrhosis, hepatocellular carcinoma and liver transplant. Retreatment due to treatment failure is not included in the model; the company suggest this pathway is ill-defined. Patients with decompensated cirrhosis do not receive any treatment. All-cause mortality is possible from any health state. Patients in more advanced liver disease states are also at increased risk of liver disease-related death. It is assumed that all recovered patients require life-long monitoring post SVR achievement, irrespective of their initial fibrosis stage.

Patient characteristics are taken from market research[22] and a prevalence study[23] conducted in the UK. Treatment characteristics, including SVR rates, treatment-related adverse events (AEs) and treatment duration are from published and unpublished clinical trials[1]. Five AEs are included in the model: anaemia, depression, rash, grade 3/4 neutropenia, and grade 3/4 thrombocytopenia. Observed SVR rates are derived from separate trials of glecaprevir/pibrentasvir and each comparator, rather than compared using network meta-analysis: SVR rates used for each treatment are summarised in Appendix Table 1. As discussed in Section 3.3, the rationale provided by the company for this approach is the lack of availability of suitable head-to-head data. In the model, these SVR rates determine the transition probabilities of patients moving from their baseline health state (mild or moderate fibrosis or compensated

cirrhosis) into the recovered health state following successful treatment. Non-treatment-specific probabilities (i.e. those determining the natural disease progression) are derived from the literature[14,24-30] or have been assumed. The hazard rates underlying transition probabilities are assumed to be constant over time. General mortality is informed by Office for National Statistics life tables for the general population[31].

The model incorporates costs associated with treatment, monitoring, adverse events, and health state. The cost of glecaprevir/pibrentasvir includes a confidential Wales Patient Access Scheme. Comparator acquisition costs are sourced from the British National Formulary (BNF)[32]. There is a PAS associated with sofosbuvir/velpatasvir. However, in keeping with AWTTC guidance, the base case uses the sofosbuvir/velpatasvir list price, and sensitivity analyses explore the effects of this discount on the cost-effectiveness of glecaprevir/pibrentasvir.

In order to calculate average treatment durations and associated costs, it is assumed that discontinuation of treatment occurs at the midpoint of trial duration. On-treatment monitoring costs are accrued according to treatment duration. These costs have been adjusted to suit peg-interferon-free regimens, but are informed by protocols based on clinical practice at Southampton University Hospital Trust[33], NICE guidelines[34] and expert opinion. Unit costs are obtained from NHS reference costs[35]. Costs associated with adverse events are obtained from a UK budget impact analysis (anaemia and rash), NICE CG90[36] and assumption (depression), NICE TA430[4] (neutropenia and thrombocytopenia) and the BNF[32] (depression, neutropenia and thrombocytopenia). Costs associated with health states are also sourced from published literature[37,38]. Where necessary, unit costs have been inflated to 2015/2016 values using the PSSRU inflation index[39].

Health state utilities are taken from published literature to capture the impact of disease progression on health related quality of life (HRQoL)[33,38,40,41]. A utility increase of 0.05 is assumed for achieving SVR for patients with mild and moderate fibrosis and compensated cirrhosis, consistent with the approach used in two prior studies[33,38]. Utility is also adjusted in the year of treatment to capture treatment-related utility impacts. For glecaprevir/pibrentasvir, these utility changes are calculated using HRQoL data collected in the clinical trials. For comparator therapies, treatment related changes in health utility are derived from published literature, where available[1]. Where no such data exists, simplifying assumptions have been applied.

Sensitivity and scenario analyses test the influence of the uncertainty associated with parameter and structural uncertainties on the robustness of the base case results. Sensitivity analyses explore the impact of varying SVR rates, adverse event rates and costs, utility values, disease progression probabilities, and health state costs. Scenario analyses explore the impact of varying discount rates on comparator treatments and use of utility values collected in the glecaprevir/pibrentasvir trials. Probabilistic sensitivity analyses have been conducted for each patient group using one comparator only, chosen on the basis of it being the next most cost-effective treatment for that group.

4.1.2 Results

The results of the base case pair-wise comparisons are detailed in Table 4. In most instances glecaprevir/pibrentasvir is estimated to be the dominant (less costly and more effective) treatment. In other comparisons the point estimates fall within the south-west quadrant of the cost-effectiveness plane (i.e. glecaprevir/pibrentasvir is shown to be less costly, but also less effective). The latter finding is particularly evident for GT4 treatment-naive patients without cirrhosis. The company estimates that in Wales, [commercial in confidence data removed] of patients are GT1 and [commercial in confidence data removed] of patients are GT3, which is consistent with other

published estimates of UK infection rates[8,42]. The results for the GT1 and GT3 patient groups generally estimate glecaprevir/pibrentasvir to be the dominant treatment.

Table 4. Results of the base case analysis

Patient population		Regimen/comparator	Total costs	Total LYG	Total QALYs	ICER (£/QALY)
GT1	TN, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
		OBV/PTV/RTV+DSV	¶¶	¶¶	¶¶	¶¶
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TN, CC	G/P	¶¶	¶¶	¶¶	-
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
		OBV/PTV/RTV+DSV	¶¶	¶¶	¶¶	¶¶
	TE, NC	G/P	¶¶	¶¶	¶¶	-
		OBV/PTV/RTV+DSV	¶¶	¶¶	¶¶	¶¶
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
	TE, CC	G/P	¶¶	¶¶	¶¶	-
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
		OBV/PTV/RTV+DSV	¶¶	¶¶	¶¶	¶¶
GT2	TN, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TN, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TE, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TE, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
GT3	TN, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TN, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TE, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TE, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
GT4	TN, NC	G/P	¶¶	¶¶	¶¶	-
		OBV/PTV/RTV	¶¶	¶¶	¶¶	¶¶
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
	TN, CC	G/P	¶¶	¶¶	¶¶	-
		OBV/PTV/RTV	¶¶	¶¶	¶¶	¶¶
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
	TE, NC	G/P	¶¶	¶¶	¶¶	-
		OBV/PTV/RTV	¶¶	¶¶	¶¶	¶¶
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
	TE, CC	G/P	¶¶	¶¶	¶¶	-
		OBV/PTV/RTV	¶¶	¶¶	¶¶	¶¶
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
		SOF/LDV	¶¶	¶¶	¶¶	¶¶
		EBR/GZR	¶¶	¶¶	¶¶	¶¶
GT5	TN, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TN, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶

Patient population		Regimen/comparator	Total costs	Total LYG	Total QALYs	ICER (£/QALY)
	TE, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TE, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
GT6	TN, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TN, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TE, NC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶
	TE, CC	G/P	¶¶	¶¶	¶¶	-
		SOF/VEL	¶¶	¶¶	¶¶	¶¶

[a]South west quadrant – therefore ICER >£20,000 per QALY foregone is desirable
¶¶: Commercial in confidence data removed.
Abbreviations: CC: compensated cirrhosis; DSV: dasabuvir; EBR/GZR: elbasvir/grazoprevir; G/P: glecaprevir/pibrentasvir; GT: genotype; ICER: incremental cost effectiveness ratio; LYG: life years gained; NC: non-cirrhotic; OBV/PTV/RTV: ombitasvir/paritaprevir/ritonavir; QALY: quality adjusted life years; SOF/LDV: sofosbuvir/ledipasvir; SOF/VEL: sofosbuvir/velpatasvir; TE: treatment experienced; TN: treatment naive.

The results of the sensitivity analyses show that the base case findings are generally most sensitive to SVR rates. However, in most instances glecaprevir/pibrentasvir remains the dominant treatment option, or the ICER produced is generally favourable for glecaprevir/pibrentasvir. Table 5 details some exceptions to this. When utility values are used from the glecaprevir/pibrentasvir trials, again glecaprevir/pibrentasvir remains the most favourable treatment option. [Commercial in confidence text removed]. When sofosbuvir/daclatasvir was included as a comparator for treatment naive GT3 patients, this did not change the findings of the base case. Table 5 details some of the more noteworthy analyses and an exploration of their plausibility. [Commercial in confidence text removed].

Table 5. Results of scenario analyses

Scenarios	ICER	Plausibility
1) GT2 TE CC – G/P v SOF/VEL Lower bound of CI of SVR for G/P used	¶¶	There is uncertainty surrounding the base case SVR estimates due to the lack of direct treatment comparison data or NMA. This scenario may therefore offer a plausible alternative but remains subject to uncertainty.
2) GT4 TE CC – G/P v OBV/PTV/RTV used a) Lower bound of CI of SVR for G/P used b) Upper bound of CI of SVR for OBV/PTV/RTV used	a) ¶¶ b) ¶¶	There is uncertainty surrounding the base case SVR estimates due to the lack of direct treatment comparison data or NMA. This scenario may therefore offer a plausible alternative but remains subject to uncertainty.
3) GT5 TN NC - G/P v SOF/VEL a) Lower bound of CI of SVR for G/P used b) Upper bound of CI of SVR for SOF/VEL used	a) ¶¶ b) ¶¶	There is uncertainty surrounding the base case SVR estimates due to the lack of direct treatment comparison data or NMA. This scenario may therefore offer a plausible alternative but remains subject to uncertainty.
4) GT5 TN CC - G/P v SOF/VEL Lower bound of CI of SVR for G/P used	¶¶	There is uncertainty surrounding the base case SVR estimates due to the lack of direct treatment comparison data or NMA. This scenario may therefore offer a plausible alternative but remains subject to uncertainty.
5) GT6 TN NC - G/P v SOF/VEL Lower bound of CI of SVR for G/P used	¶¶	There is uncertainty surrounding the base case SVR estimates due to the lack of direct treatment comparison data or NMA. This scenario may therefore offer a plausible alternative but remains subject to uncertainty.
6) GT6 TN CC - G/P v SOF/VEL Lower bound of CI of SVR for G/P used	¶¶	There is uncertainty surrounding the base case SVR estimates due to the lack of direct treatment comparison data or NMA. This scenario may therefore offer a plausible alternative but remains subject to uncertainty.
7) GT6 TE CC - G/P v SOF/VEL Lower bound of CI of SVR for G/P used	¶¶	There is uncertainty surrounding the base case SVR estimates due to the lack of direct treatment comparison data or NMA. This scenario may therefore offer a plausible alternative but remains subject to uncertainty.

[Commercial in confidence text removed].
¶¶: Commercial in confidence data removed
Abbreviations: CC: compensated cirrhosis; CI: confidence interval; GT: genotype; G/P: glecaprevir/pibrentasvir; ICER: incremental cost effectiveness ratio; NC: non-cirrhotic; OBV/PTV/RTV: ombitasvir/paritaprevir/ritonavir; SVR: sustained virologic response; TE: treatment experienced; TN: treatment naïve; SOF/VEL: sofosbuvir/velpatasvir.

The probabilistic sensitivity analyses reveal that when glecaprevir/pibrentasvir is compared with the next most cost-effective comparator for each patient group, the probability of being cost-effective is between [commercial in confidence data removed] at a willingness to pay (WTP) threshold of £20,000. If the WTP threshold is increased to £30,000, the probability of glecaprevir/pibrentasvir being the most cost effective treatment ranges from [commercial in confidence data removed].

4.1.3 AWTTC critique

The reliability of the CUA is highly dependent on the accuracy of SVR rates included in the model, and these are subject to uncertainty. The analyses suggest that glecaprevir/pibrentasvir is likely to be the most cost-effective treatment option for GT1 and GT3 patients, who make up the majority of this patient population in Wales and this result appears to be robust.

Strengths of the cost-effectiveness analysis include:

- The submission gives a detailed, transparent account of most of the methods and data sources used in the analysis.
- The model structure is built on previously published models[38,43,44] of the natural history of HCV infection. The company also offer justifications for the assumptions underpinning the model.
- The submission includes an extensive number of comparative analyses by patient population.

Limitations of the cost-effectiveness analysis include:

- The efficacy data used in the analyses are not derived from network meta-analyses. Instead, unadjusted comparisons are used. SVR rates are taken from a number of studies, some of which are unpublished, and in some cases use small subgroups of the overall trial population. Whilst this means there is more uncertainty around estimates of comparative clinical effectiveness, this approach has been used in health technology assessments of other HCV treatments that are recommended for use by AWMSG[19] and NICE[4].
- Base case health state utility values are taken from the published literature rather than the data collected in the glecaprevir/pibrentasvir trials. Generally, the use of primary data is preferred to secondary data in economic analyses, as it facilitates a better evaluation of the relationship between costs and effects in the group of interest. However, the company conducted additional scenario analyses upon AWTTC request to explore the use of the values collected in the glecaprevir/pibrentasvir trials. These revealed no meaningful change from the base case.
- Transition probabilities are informed by a number of studies and assumptions. There is uncertainty surrounding these values, given that the studies have been conducted in a variety of settings, with differing patient populations, and that assumptions are inherently associated with uncertainty**.**
- Medicine acquisition costs are calculated using average treatment durations from trials. It is unclear to what extent these data reflect real-world medicine use.
- Neither re-infection nor onward transmission is included in the model. Similarly, the strategy of opting to delay the initiation of treatment until liver disease progresses is not reflected. It is uncertain what effects their inclusion would have on the results of the analyses.

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 estimate that 12,000 people in Wales have chronic HCV infection, based on the Welsh Government Liver Disease Delivery Plan[9]. It is assumed that the prevalence remains constant over time, given that the Welsh Government intends to treat 900 HCV patients per year. The company forecast that glecaprevir/pibrentasvir will become the first-line treatment for [commercial in confidence data removed] of patients, which equates to [commercial in confidence data removed] patients per year. Sensitivity analyses explore the impact of varying the expected uptake by ±10%, all other things being equal. Scenario analyses are conducted to explore the impact of the patient access scheme associated with sofosbuvir/velpatasvir on the results, in addition to the exclusion of sofosbuvir plus daclatasvir (with or without ribavirin) from the comparator treatment group.

5.1.2 Results

The estimated budget impact is presented in Table 6. The company estimates that the introduction of glecaprevir/pibrentasvir would lead to an overall [commercial in confidence data removed] each year, and a total [commercial in confidence dara removed] over five years. This estimate incorporates cost differences resulting from the displacement of alternative treatments, as [commercial in confidence text removed]. No other costs are considered in the analyses. The company sensitivity analyses further support the finding that the introduction of glecaprevir/pibrentasvir would likely be associated with [commercial in confidence text removed]. When uptake for glecaprevir/pibrentasvir is varied by ±10%, this results in [commercial in confidence data removed]. The company has not evaluated the likely net resource implications arising from the introduction of glecaprevir/pibrentasvir.

Table 6. Company-reported costs associated with use of glecaprevir/pibrentasvir for the treatment of HCV

	Year 1 (2017)	Year 2 (2018)	Year 3 (2019)	Year 4 (2020)	Year 5 (2021)
Number of eligible patients (Indication covered in this submission)	900	900	900	900	900
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Treated patients	¶¶	¶¶	¶¶	¶¶	¶¶
Net medication acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: Commercial in confidence data 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 glecaprevir/pibrentasvir.
- The model assumes a constant prevalence of chronic HCV infection aligned to Welsh Government treatment plans. Successful treatment and management, however, should lead to a reduction of HCV over time. The current plan is to eliminate the virus by or before 2030 in Wales[45]. How prevalence will be influenced in the interim is uncertain however, and the omission of this effect is an acceptable simplification.
- The budget impact model includes sofosbuvir plus daclatasvir and ribavirin as a comparator for the base case, unlike the main economic model. Its inclusion biases the base case results in favour of glecaprevir/pibrentasvir. However, the effects of

its inclusion are minimal; its exclusion reduced the predicted savings by less than 0.2%.

- The company predict a constant annual uptake of [commercial in confidence data removed]_for glecaprevir/pibrentasvir. The rationale for this uptake has not been fully explained, and it is therefore unclear how realistic the projected net savings are.
- Net resource costs due to adverse events and monitoring have not been determined in the model. It is plausible that resources may be saved for patients where glecaprevir/pibrentasvir displaces a medicine associated with a less favourable adverse events profile. Similarly, in patients eligible to receive glecaprevir/pibrentasvir for 8 weeks, monitoring costs may be lower than those associated with the comparators requiring longer treatment durations.
- The company suggest that if glecaprevir/pibrentasvir were to become the default treatment in Wales, the need for genotype testing would be significantly reduced, and that the favourable safety and tolerability profile of glecaprevir/pibrentasvir may enable service redesign (e.g. reduced monitoring). The budget impact model does not explore this potential.

5.2 Comparative unit costs

Table 7. Examples of medicine acquisition costs per course of treatment with glecaprevir/pibrentasvir and alternative chronic HCV treatment regimens (for patients without cirrhosis or with compensated cirrhosis)

Treatment regimen	Genotype	Example doses	Duration of treatment	Approximate regimen costs per patient
G/P	GT1–6	300 mg/120 mg OD	8 weeks	¶¶
			12 weeks	¶¶
			16 weeks	¶¶
OBV/PTV/RTV + DSV ± RBV	GT1	OBV 25 mg / PTV 150 mg / RTV 100 mg OD, DSV 250 mg BD, ± RBV 1,000 mg OD	12 weeks	£35,000–£35,804
			24 weeks	£70,000–£71,608
OBV/PTV/RTV+RBV	GT4	OBV 25 mg / PTV 150 mg / RTV 100 mg OD+RBV 1,000 mg OD	12 weeks	£33,004
SOF/VEL	GT1–6	400 mg/100 mg OD	12 weeks	£38,980
EBR/GZR	GT1, GT4	GZR 100 mg / EBR 50 mg OD	12 weeks	£36,500
SOF/LDV ± RBV	GT1, GT4	SOF 400 mg / LDV 90 mg OD, ± RBV 1,000 mg OD	8 weeks	£25,987–£26,522
			12 weeks	£38,980–£39,784
SOF + DCV ± RBV	GT3	SOF 400 mg OD, DCV 60 mg OD ± RBV 1,000 mg OD	12 week	£59,501[a]
			24 weeks	£119,002–£120,610

Cost of G/P has been provided by the company. Costs of comparators are based on MIMS list prices as of 8 June 2017, although it should be noted that SOF/VEL is associated with a Patient Access Scheme. Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.
BD: twice daily; DCV: daclatasvir; DSV: dasabuvir; EBR/GZR: elbasvir/grazoprevir; G/P: glecaprevir/pibrentasvir; OBV/PTV/RTV: ombitasvir/paritaprevir/ritonavir; OD: once daily; SOF/LDV: sofosbuvir/ledipasvir; SOF/VEL: sofosbuvir/velpatasvir; RBV: ribavirin.
Ribavirin doses are based on patients weighing <75kg
[a]Licence for SOF + DCV for GT3 12 week regimen does not include RBV.
¶¶: Commercial in confidence data removed

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

6.2 Ongoing studies

The company submission highlighted the following ongoing studies for which results are likely to be available within 6–12 months[1]:

- Long term outcomes study: M13-576: A follow-up study to assess resistance and durability of response to AbbVie direct-acting antiviral agent therapy (ABT-493 and/or ABT-530) in patients who participated in phase II or III clinical studies for the treatment of chronic HCV infection

- Paediatric study: M16-123: A study to evaluate the pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in paediatric patients with genotypes 1-6 chronic HCV infection
- Prior AbbVie DAA virologic failure study: M15-942: An open-label, multicentre study to evaluate the efficacy and safety of ABT-493/ABT-530 in combination with sofosbuvir and ribavirin in chronic HCV-infected patients who have experienced virologic failure in AbbVie HCV clinical studies (MAGELLAN-3)
- NC study: M16-133: Single arm, open-label, multicentre study to evaluate the efficacy and safety of AbbVie HCV DAAs in treatment-naïve adults with HCV genotypes 1–6 infection and an aspartate aminotransferase/platelet ratio index (APRI) ≤1
- CC study: M16-135: A single arm, open-label study to evaluate the efficacy and safety of glecaprevir/pibrentasvir in treatment-naïve adults with chronic HCV genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis

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: 13 June 2017
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1. AbbVie Ltd. Form B: Detailed appraisal submission. Glecaprevir/pibrentasvir (Maviret®). May 2017.
2. AbbVie Ltd. Maviret®. Summary of Product Characteristics. Jul 2017. Accessed Jul 2017.
3. European Association for the Study of the Liver (EASL). EASL recommendations on treatment of hepatitis C 2016. *Journal of Hepatology* 2017;66:153-194. Available at: http://www.easl.eu/medias/cpg/HCV2016/English-report.pdf. Accessed Jul 2017.
4. National Institute for Health and Care Excellence. Technology Appraisal TA430. Sofosbuvir–velpatasvir for treating chronic hepatitis C. Jan 2017. Available at: https://www.nice.org.uk/guidance/ta430. Accessed May 2017.
5. The Hepatitis C Trust. About Hepatitis C. 2014. Available at: http://www.hepctrust.org.uk/about-hepatitis-c. Accessed Jul 2017.
6. Chen SL, and Morgan TR. The natural history of hepatitis C virus (HCV) infection. *International Journal of Medical Sciences.* 2006;3(2):47-52.
7. The Hepatitis C Trust. Compensated cirrhosis. 2015. Available at: http://hepctrust.nam.org.uk/compensated-cirrhosis. Accessed Jul 2017.
8. Public Health England. Hepatitis C in the UK. 2015 report. Jul 2015. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448710/NEW_FINAL_HCV_2015_IN_THE_UK_REPORT_28072015_v2.pdf. Accessed Aug 2017.
9. Welsh Government. Together for Health. Liver disease annual report 2016 - setting the baseline. 2016. Available at: http://gov.wales/topics/health/nhswales/plans/liver-disease/?lang=en. Accessed Jul 2016.
10. National Institute for Health Research (NIHR). Glecaprevir with pibrentasvir for chronic hepatitis C infection, genotypes 1, 2, 3, 4, 5 and 6. April 2016. Available at: http://www.io.nihr.ac.uk/topics/glecaprevir-with-pibrentasvir-for-chronic-hepatitis-c-infection-genotypes-1-2-3-4-5-and-6/. Accessed Jul 2017.
11. National Institute for Health and Care Excellence. Technology Appraisal TA413. Elbasvir–grazoprevir for treating chronic hepatitis C. Jul 2017. Available at: https://www.nice.org.uk/guidance/ta413. Accessed May 2017.
12. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. Apr 2016. Available at: http://apps.who.int/iris/handle/10665/205035. Accessed Jul 2016.
13. National Institute for Health and Care Excellence. Technology Appraisal TA365. Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C. Nov 2015. Available at: https://www.nice.org.uk/guidance/ta365. Accessed Jul 2017.
14. National Institute for Health and Care Excellence. Technology Appraisal TA364. Daclatasvir for treating chronic hepatitis C. Nov 2015. Available at: https://www.nice.org.uk/guidance/ta364. Accessed Jul 2017.
15. National Institute for Health and Care Excellence. Technology Appraisal TA363. Ledipasvir–sofosbuvir for treating chronic hepatitis C. Nov 2015. Available at: https://www.nice.org.uk/guidance/ta363. Accessed Jul 2017.
16. National Institute for Health and Care Excellence. Technology Appraisal TA331. Simeprevir in combination with peginterferon alfa and ribavirin for treating genotypes 1 and 4 chronic hepatitis C. Feb 2015. Available at: https://www.nice.org.uk/guidance/ta331. Accessed Jul 2017.
17. All Wales Medicines Strategy Group. Ledipasvir/sofosbuvir (Harvoni®) 90 mg/400 mg film-coated tablet. Reference number: 1887. Appraisal information. Aug 2015. Available at:

http://www.awmsg.org/awmsgonline/app/appraisalinfo/1887. Accessed Jul 2017.
18. All Wales Medicines Strategy Group. Daclatasvir (Daklinza®) 30 mg and 60 mg film-coated tablets. Reference number: 1464. Appraisal information. May 2015. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1464. Accessed Jul 2017.
19. All Wales Medicines Strategy Group. Sofosbuvir/velpatasvir (Epclusa®) 400 mg/100 mg film-coated tablet. Reference number: 2417. Appraisal information. Nov 2016. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/2417. Accessed May 2017.
20. National Institute for Health and Care Excellence. Single Technology Appraisal. Sofosbuvir-velpatasvir for treating chronic hepatitis C. Final scope. Mar 2016. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10064/documents. Accessed Jul 2017.
21. National Institute for Health and Care Excellence. Single Technology Appraisal. Glecaprevir with pibrentasvir for treating chronic hepatitis C. Final scope. May 2017. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10169. Accessed Jul 2017.
22. Adelphi Research UK. Patient tracker, Project reference 22968. 2017. Accessed July 2017.
23. Harris KA, Gilham C, Mortimer PP et al. The most prevalent hepatitis C virus genotypes in England and Wales are 3a and 1a. *Journal of medical virology.* 1999;58(2):127-131.
24. Bennett WG, Inoue Y, Beck JR et al. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Annals of internal medicine.* 1997;127(10):855-865.
25. Cardoso AC, Moucari R, Figueiredo-Mendes C et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol.* 2010;52(5):652-657.
26. Fattovich G, Giustina G, Degos F et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology.* 1997;112(2):463-472.
27. Grieve R, Roberts J, Wright M et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut.* 2006;55(9):1332-1338.
28. Kanwal F, Kramer JR, Ilyas J et al. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. *Hepatology (Baltimore, Md.).* 2014;60(1):98-105.
29. Siebert U, Sroczynski G, Rossol S et al. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut.* 2003;52(3):425-432.
30. Thein HH, Yi Q, Dore GJ et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology (Baltimore, Md.).* 2008;48(2):418-431.
31. Office for National Statistics. National life tables, UK: 2013–2015. 2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/20132015. Accessed July 2017.
32. British Medical Association, and Royal Pharmaceutical Society of Great Britain. British National Formulary. July 2017. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed July 2017.
33. Shepherd J, Jones J, Hartwell D et al. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health technology assessment (Winchester, England).* 2007;11(11):1-205, iii.

34. National Institute for Health and Care Excellence. NICE Guideline, CG165. Hepatitis B (chronic): diagnosis and management. June 2013. Available at: https://www.nice.org.uk/guidance/cg165. Accessed July 2017.
35. Department of Health. NHS Reference Costs 2015-16. 2016. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016. Accessed July 2017.
36. National Institute for Health and Care Excellence. NICE Guideline, CG90. Depression in adults: recognition and management. April 2016. Available at: https://www.nice.org.uk/guidance/cg90. Accessed July 2017.
37. Backx M, Lewszuk A, White JR et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *Journal of viral hepatitis.* 2014;21(3):208-215.
38. Hartwell D, Jones J, Baxter L et al. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health technology assessment (Winchester, England).* 2011;15(17):i-xii, 1-210.
39. Curtis L, and Burns A. Unit Costs of health and Social Care. 2016. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2016/. Accessed July 2017.
40. Ratcliffe J, Longworth L, Young T et al. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society.* 2002;8(3):263-270.
41. Wright M, Grieve R, Roberts J et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health technology assessment (Winchester, England).* 2006;10(21):1-113, iii.
42. Petruzziello A, Marigliano S, Loquercio G et al. Hepatitis C virus (HCV) genotypes distribution: an epidemiological up-date in Europe. *Infectious agents and cancer.* 2016;11:53. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5062817/pdf/13027_2016_Article_99.pdf.
43. Johnson SJ, Parise H, Virabhak S et al. Economic evaluation of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic genotype 1 hepatitis c virus infection. *Journal of medical economics.* 2016;19(10):983-994.
44. Liu S, Cipriano LE, Holodniy M et al. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Annals of internal medicine.* 2012;156(4):279-290.
45. The Hepatitis C Trust. Hepatitis C in Wales: Perspectives, challenges & solutions. 2016. Available at: http://www.hepctrust.org.uk/sites/default/files/Hepatitis%20C%20in%20Wales%20-%20Perspectives%2C%20Challenges%20%26%20Solutions_0.pdf. Accessed Jul 2017.

Appendix. Additional clinical outcomes

Table 1. Estimated 12-week sustained virologic response rates for glecaprevir/pibrentasvir and comparator treatments[1]

Genotype	Treatment status	No cirrhosis[a]		Cirrhosis[b]	
		Treatment and duration	SVR12, % (n/N)	Treatment and duration	SVR12, % (n/N)
GT1	Naive	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		OBV/PTV/RTV + DSV (GT1b) + RBV (GT1a), both 12 wks	¶¶[c]	OBV/PTV/RTV + DSV, 12 wks (GT1b) + RBV, 24 wks (GT1a)	¶¶[c]
		EBR/GZR, 12 wks	93.2% (NR)[c]	EBR/GZR, 12 wks	95.9% (NR)[c]
		SOF/LDV, 8 wks	F0 – F1: 95.2% (80/84) F2 – F3: 94.4% (68/72)	SOF/LDV, 12 wks	94.1% (32/34)
		SOF/VEL, 12 wks	98.4% (251/255)	SOF/VEL, 12 wks	98.6% (72/73)
	Experienced	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		OBV/PTV/RTV + DSV (GT1a) + RBV (GT1b), both 12 wks	97.4% (NR)[c]	OBV/PTV/RTV + DSV, 12 wks (GT1b) + RBV, 24 wks (GT1a)	98.5% (NR)[c]
		EBR/GZR, 12 wks	93.4% (NR)[c]	EBR/GZR, 12 wks	93.2% (NR)[c]
		SOF/LDV, 12 wks	95.4% (83/87)	SOF/LDV, 12 wks	86.4% (19/22)
		SOF/VEL, 12 wks	98.4% (251/255)	SOF/VEL, 12 wks	98.6% (72/73)
GT2	Naive	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		SOF/VEL, 12 wks	99.0% (99/100)	SOF/VEL, 12 wks	100.0% (15/15)
	Experienced	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		SOF/VEL, 12 wks	100.0% (15/15)	SOF/VEL, 12 wks	100.0% (4/4)

Genotype	Treatment status	No cirrhosis[a]		Cirrhosis[b]	
		Treatment and duration	SVR12, % (n/N)	Treatment and duration	SVR12, % (n/N)
GT3	Naive	G/P, 8 wks	94.9% (149/157)	G/P, 12 wks	¶¶
		SOF/VEL, 12 wks	98.2% (160/163)	SOF/VEL, 12 wks	93.0% (40/43)
		SOF + DCV, 12 wks	96.8% (184/190)[e]	SOF + DCV + RBV, 24 wks	100% (5/5)
	Experienced	G/P, 16 wks	95.5% (21/22)	G/P, 16 wks	¶¶
		SOF/VEL, 12 wks	91.2% (31/34)	SOF/VEL, 12 wks	89.2% (33/37)
		SOF + DCV ± RBV, 12 wks	94.1% (32/34)	SOF + DCV + RBV, 24 wks	100% (5/5)
GT4	Naive	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		OBV/PTV/RTV + RBV, 12 wks	100.0% (42/42)	OBV/PTV/RTV + RBV, 12 wks	96.7% (29/30)
		EBR/GZR, 12 wks	100.0% (16.71/16.71)[d]	EBR/GZR, 12 wks	100.0% (1.29/1.29)[d]
		SOF/LDV, 12 wks	95.2% (20/21)	SOF/LDV, 12 wks	100.0% (1/1)
		SOF/VEL, 12 wks	100.0% (89/89)	SOF/VEL, 12 wks	100.0% (27/27)
	Experienced	G/P, 8 wks	¶¶	G/P, 8 wks	¶¶
		OBV/PTV/RTV + RBV, 12 wks	100.0% (49/49)	OBV/PTV/RTV + RBV, 12 wks	98.2% (N=29)[e]
		EBR/GZR, 12 wks	100.0% (3/3)	EBR/GZR, 12 wks	66.7% (4/6)
		SOF/LDV, 12 wks	84.6% (11/13)	SOF/LDV, 12 wks	100.0% (9/9)
		SOF/VEL, 12 wks	100.0% (89/89)	SOF/VEL, 12 wks	100.0% (27/27)
GT5	Naive	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		SOF/VEL, 12 wks	96.6% (28/29)	SOF/VEL, 12 wks	100.0% (5/5)
	Experienced	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		SOF/VEL, 12 wks	100.0% (11/11)	SOF/VEL, 12 wks	100.0% (11/11)

Genotype	Treatment status	No cirrhosis[a]		Cirrhosis[b]	
		Treatment and duration	SVR12, % (n/N)	Treatment and duration	SVR12, % (n/N)
GT6	Naive	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		SOF/VEL, 12 wks	100.0% (35/35)	SOF/VEL, 12 wks	100.0% (6/6)
	Experienced	G/P, 8 wks	¶¶	G/P, 12 wks	¶¶
		SOF/VEL, 12 wks	100.0% (35/35)	SOF/VEL, 12 wks	100.0% (6/6)

[a]Defined as a METAVIR score F0—F3 (no fibrosis to moderate fibrosis). [b]Defined as a METAVIR score F4 (indicating cirrhosis). [c]Calculated using a weighted average of SVRs from different studies/populations. n/N is not reported. [d]The number of GT4 patients with and without CC has been estimated and reported to 2 decimal places. [e]Only the SVR rate and the total number of patients were reported.

¶¶: Commercial in confidence data removed.

Abbreviations: CC: compensated cirrhosis; DAA: direct-acting antiviral; DSV: dasabuvir; EBR/GZR: elbasvir/grazoprevir; G/P: glecaprevir/pibrentasvir; GT: genotype; HCV: hepatitis C virus; NC: non-cirrhotic; OBV/PTV/RTV: ombitasvir/paritaprevir/ritonavir; SVR: sustained virologic response; TE-PR: treatment-experienced with regimens containing peginterferon and/or ribavirin; TE-PRS: treatment-experienced with regimens containing interferon; TN: treatment-naïve; SOF/LDV: sofosbuvir/ledipasvir, SOF/VEL: sofosbuvir/velpatasvir; RBV: ribavirin.