SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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glecaprevir 100mg, pibrentasvir 40mg film-coated tablet (Maviret®)

SMC No 1278/17

AbbVie Ltd

6 October 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

glecaprevir-pibrentasvir (Maviret®) is accepted for use within NHS Scotland.

Indication under review: Treatment of chronic hepatitis C virus (HCV) infection in adults.

Glecaprevir-pibrentasvir is associated with high rates of sustained virologic suppression in patients with all genotypes of chronic HCV infection. In treatment-naïve non-cirrhotic patients with genotype 3 infection it was non-inferior to a direct acting anti-viral regimen that included a non-structural protein 5B (NS5B) inhibitor plus NS5A inhibitor.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of glecaprevir-pibrentasvir. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 November 2017

Indication

Treatment of chronic hepatitis C virus (HCV) infection in adults.[1]

Dosing Information

Three tablets swallowed whole once daily with food. The tablets should not be chewed, crushed or broken as this can alter the bioavailability of the medicines.[1]

For treatment-naive patients who have GT1 to 6 infection and treatment-experienced patients (previously given peginterferon or sofosbuvir in combination with ribavirin or all three medicines) who have GT1, 2, 4, 5 or 6 infection, treatment is continued for eight weeks in those with no cirrhosis and for 12 weeks in those with compensated cirrhosis.

For treatment-experienced (previously given peginterferon or sofosbuvir in combination with ribavirin or all three medicines) patients with GT3 infection treatment is continued for 16 weeks in those without and with compensated cirrhosis, including those who have received a liver transplant.

For other patients who have received a liver transplant, treatment should be continued for a minimum of 12 weeks.[1]

Glecaprevir-pibrentasvir is not recommended for re-treatment of patients with prior exposure to NS3/4A-inhibitors and/or NS5A-inhibitors or for patients with moderate hepatic impairment (Child-Pugh B). It is contra-indicated in patients with severe hepatic impairment (Child-Pugh C).[1]

Treatment with glecaprevir-pibrentasvir should be initiated and monitored by a physician experienced in the management of patients with HCV infection.[1]

Product availability date

July 2017

Glecaprevir-pibrentasvir received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 9th May 2017. The scientific opinion was for the treatment of chronic HCV infection in adults with compensated cirrhosis and at least one of the following:

- genotypes 1, 4, 5 and 6 with compensated cirrhosis previously treated with NS5A inhibitors
- genotypes 2, 3, 5 or 6 with chronic kidney disease (stage 4 and 5)
- GT-3 infected patients previously treated with peginterferon, ribavirin, and/or sofosbuvir

(Note that the final marketing authorisation does not include re-treatment of patients with prior exposure to NS5A-inhibitors)

Summary of evidence on comparative efficacy

Glecaprevir-pibrentasvir (Maviret®) is a fixed-dose formulation of a non-structural protein (NS5A) inhibitor (pibrentasvir) and a NS3/4A protease inhibitor (glecaprevir) licensed for treatment of all genotypes (GT1 to 6) of chronic hepatitis C virus (HCV) infection.[1]

Seven phase III studies recruited adults with chronic HCV infection. All were open-label except a double-blind comparison with placebo (ENDURANCE-2). The ENDURANCE-1, -2, -3 and -4 studies included patients who had GT 1, 2, 3 and 4 to 6, respectively, without cirrhosis and who were treatment-naive or treatment-experienced (to interferon or peg-interferon ± ribavirin or sofosbuvir plus ribavirin ± peg-interferon), except ENDURANCE-3, which only included treatment-naive patients. The EXPEDITION-1, -2 and -4 studies recruited patients with GT1 to 6, without or with compensated cirrhosis, who were treatment-naive or treatment-experienced (as defined above), except for EXPEDITION-1, which excluded patients with GT3 and those without cirrhosis. EXPEDITION-2 also required that patients were co-infected with human-immunodeficiency virus (HIV) and EXPEDITION-4 required that patients had severe renal impairment, chronic kidney disease (CKD) stage 4 or 5.[2-17]

In ENDURANCE-1 randomisation was stratified by viral load (< or ≥ 6million IU/mL) and HCV GT1 subtype (1b or non-1b), then patients were assigned equally to open-label 8-week or 12-week glecaprevir-pibrentasvir 300mg/120mg once daily. In ENDURANCE-2 randomisation was stratified by last previous treatment (naïve versus peg-interferon ± ribavirin versus sofosbuvir plus ribavirin ± peg-interferon) and patients were assigned in a 2:1 ratio to double-blind 12-week glecaprevir-pibrentasvir 300mg/120mg once daily or placebo. In ENDURANCE-3 patients were initially randomised in a 2:1 ratio to open-label 12-week glecaprevir-pibrentasvir 300mg/120mg once daily or 12-week sofosbuvir 400mg plus daclatasvir 60mg once daily. After enrolment in these two groups was complete, patients were assigned to a third group, 8-week glecaprevir-pibrentasvir 300mg/120mg once daily. In the other four studies patients received open-label 12-week glecaprevir-pibrentasvir 300mg/120mg once daily, except non-cirrhotic patients in EXPEDITION-2, who received this for 8 weeks.[2-17]

In all studies the primary outcome was sustained virologic response (SVR), defined as HCV RNA below the lower limit of quantification, 12 weeks after the end of treatment (SVR12). This was assessed in all patients who received at least one dose of study drug, except in the ENDURANCE-1 and -2 studies where it was primarily assessed in those who were direct-acting antiviral (DAA)-naïve and in ENDURANCE-1 without HIV.[2-17]

ENDURANCE-1. In non-cirrhotic patients with GT1 chronic HCV infection (who were DAA-naive and not co-infected with HIV, i.e. ITT-PS population), 12-week glecaprevir-pibrentasvir SVR12 of 99.7% (331/332) with 95% confidence interval (CI) 99.1% to 100% was non-inferior to a historical control as the lower bound of the 95% CI exceeded 91%. For glecaprevir-pibrentasvir regimens, 8-week was non-inferior to 12-week in the ITT-PS-per protocol population (100% [332/332] versus 100% [331/331]) and in ITT-PS (99.1% [332/335] versus 99.7% [331/332]).[3]

ENDURANCE-2. In non-cirrhotic patients with GT2 chronic HCV infection (who were DAA-naive), 12-week glecaprevir-pibrentasvir SVR12 of 99.5% (195/196) was non-inferior to a historical control as the lower bound of the 95% CI exceeded 89%.[5]

ENDURANCE-3. In non-cirrhotic treatment-naive patients with GT3 chronic HCV infection, 12-week glecaprevir-pibrentasvir was non-inferior to 12-week sofosbuvir plus daclatasvir for SVR12: 95.3% (222/233) and 96.5% (111/115), respectively. The 8-week glecaprevir-pibrentasvir regimen, which had SVR12 of 94.9% (149/157), was non-inferior to 12-week glecaprevir-pibrentasvir.[8]

ENDURANCE-4: In non-cirrhotic patients with GT4 to 6 chronic HCV infection, the SVR12 with 12-week glecaprevir-pibrentasvir was 99.2% (120/121).[10]

EXPEDITION-1: In patients with Child-Pugh A compensated cirrhosis and GT1, 2 or 4 to 6 chronic HCV infection, SVR12 with 12-week glecaprevir-pibrentasvir was 99.3% (145/146).[12]

EXPEDITION-2: In patients without cirrhosis who had GT1 to 6 chronic HCV and HIV infection, SVR12 with 8-week glecaprevir-pibrentasvir was 99.3% (136/137). In patients with compensated cirrhosis who had GT1 to 4 chronic HCV and HIV infection the SVR with 12-week glecaprevir-pibrentasvir was 87.5% (14/16).[14]

EXPEDITION-4: In patients without cirrhosis (81% of study population) or with compensated cirrhosis (19% of study population) who had GT1 to 6 chronic HCV infection and severe renal impairment, SVR12 with 12-week glecaprevir-pibrentasvir was 98.1% (102/104).[16]

For the ENDURANCE and EXPEDITION studies analyses by genotype are detailed in table 1.

Table 1: SVR12 by genotype in the ENDURANCE and EXPEDITION studies

	SVR12					
	GT1	**GT2**	**GT3**	**GT4**	**GT5**	**GT6**
ENDURANCE-1, -2, 3, and 4 for non-cirrhotic GT1, GT2, GT3 and GT4-6, respectively.						
G-P 8wks	99.1% (332/335)	-	94.9% (149/157)	-	-	-
G-P 12wks	99.7% (331/332)	99.5% (195/196)	95.3% (222/233)	98.7% (75/76)	100% (26/26)	100% (19/19)
S-D 12wks	-	-	96.5% (111/115)	-	-	-
EXPEDITION-1 for Child-Pugh A compensated cirrhosis GT1, 2, 4-6						
G-P 12wks	98.8% (86/87)	100% (34/34)	-	100% (16/16)	100% (2/2)	100% (7/7)

G-P = glecaprevir-pibrentasvir 300mg/120mg once daily; S-D = sofosbuvir 400 mg plus daclatasvir 60 mg once daily

Several groups from the open-label phase II SURVEYOR-2 study provide data on relevant doses of glecaprevir-pibrentasvir. This study provides the main evidence for the primary outcome of SVR12 in difficult to treat GT3 infection, i.e. in patients with cirrhosis and/or treatment-experienced (to peg-interferon plus ribavirin). For regimens licensed for GT3, SVR12 rates combined from relevant treatment groups were 98% (64/65) for 12-week glecaprevir-pibrentasvir in treatment-naïve adults with cirrhosis; 95% (21/22) and 94% (48/51) for 16-week glecaprevir-pibrentasvir in treatment-experienced adults without and with cirrhosis, respectively.[1,2,18-20]

On-treatment virologic failure in ENDURANCE-3, which recruited patients with GT3, occurred in one patient receiving 8-week glecaprevir-pibrentasvir and in one patient receiving 12-week glecaprevir-pibrentasvir. There were no on-treatment virologic failures with sofosbuvir plus daclatasvir. Virologic failure due to relapse occurred in 3.2% (5/157), 1.3% (3/233) and 0.9% (1/115) of GT3 patients with 8-week and 12-week glecaprevir-pibrentasvir and 12-week sofosbuvir plus daclatasvir, respectively.[2-20]

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

Summary of evidence on comparative safety

The safety assessment in the summary of product characteristics (SPC) included approximately 2,300 patients given glecaprevir-pibrentasvir for 8-, 12- or 16-weeks in phase II and III studies. The most common adverse events were headache and fatigue, with other commonly reported adverse events including diarrhoea, nausea and asthenia. Serious adverse events (transient ischaemic attack) were reported by less than 0.1% of patients and 0.1% of patients prematurely discontinued treatment.[1]

In the active-controlled study, ENDURANCE-3, there was a comparable rate of adverse events in the 12-week glecaprevir-pibrentasvir and sofosbuvir plus daclatasvir groups: 76% (177/233) and 70% (80/115). Within the respective 8-week and 12-week glecaprevir-pibrentasvir groups and the 12-week sofosbuvir plus daclatasvir group there were similar rates of serious adverse events, 1.9% (3/157), 2.1% (5/233) and 1.7% (2/115); and adverse events leading to study drug discontinuation, 0, 1.3% (3/233) and 0.9% (1/115). Overall a similar adverse event profile was observed across all treatment groups, with the most common adverse events being, headache (20%, 26% and 20%), fatigue (13%, 19% and 14%) and nausea (12%, 14 and 13%).[2,8,9]

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

Summary of clinical effectiveness issues

Glecaprevir-pibrentasvir (Maviret®) a fixed-dose formulation of NS5A inhibitor (pibrentasvir) and NS3/4A protease inhibitor (glecaprevir) is the third regimen (after Viekirax® and Zepatier®) containing a NS5A and NS3/4A inhibitor licensed in the UK for HCV infection, but the first with this pharmacology to be licensed in the UK for all genotypes, GT1 to 6.[1] Other regimens licensed for use in all or almost all GT of HCV are Epclusa® (fixed-dose formulation of NS5A inhibitor, velpatasvir, and NS5B inhibitor, sofosbuvir), licensed for GT1 to 6 and Harvoni® (fixed dose formulation of NS5A inhibitor, ledipasvir and NS5B inhibitor, sofosbuvir), licensed for use in GT1, 3, 4, 5 and 6.[21,22] Clinical experts consulted by SMC noted the current lack of DAA treatment options in patients infected with GT2, 3, 5 and 6 with chronic kidney disease (stage 4 and 5) and also the lack of retreatment options for patents who have previously failed on a DAA regimen.

HCV is a blood borne viral infection that can lead to liver cirrhosis and hepatocellular carcinoma. The national clinical guideline for the treatment of HCV in adults provides guidance on the place in therapy of currently available medicines. The guideline, published in January 2017, is based on the principle developed by HCV Treatment and Therapies Sub-group of the National Sexual Health and Blood Borne Virus Advisory Committee, which states that patients should expect that the likelihood of cure with their initial treatment is at least 90% and this should be achieved with

minimal side effects. The guideline advice is detailed below in additional information: guidelines and protocols section.[23]

In the phase III ENDURANCE-1 study 8-week glecaprevir-pibrentasvir (which is the licensed regimen for patients without cirrhosis) and 12-week glecaprevir-pibrentasvir were associated with high SVR12 rates in GT1 patients without cirrhosis who were treatment-naïve or treatment-experienced with prior exposure to peginterferon plus ribavirin. In the other three phase III ENDURANCE studies (-2, -3 and -4) 12-week glecaprevir-pibrentasvir (which is not the recommended regimen for patients without cirrhosis) was associated with high SVR12 rate in GT2, GT3 and GT4 to 6 patients, respectively, without cirrhosis who were treatment-naïve and, in ENDURANCE-2 and -4, were treatment-experienced with prior exposure to peginterferon plus ribavirin. In ENDURANCE-3, in treatment-naïve non-cirrhotic GT3 patients, the SVR12 with 12-week glecaprevir-pibrentasvir was non-inferior to 12-week sofosbuvr plus daclatasvir and 8-week glecaprevir-pibrentasvir was non-inferior to 12-week glecaprevir-pibrentasvir. The phase III studies provide no evidence of efficacy in GT3 patients who are treatment-experienced and very little evidence in GT3 patients with cirrhosis.

Evidence of efficacy in GT3, which can be a difficult genotype to cure, within patients who are at higher risk of treatment-failure, i.e. with cirrhosis and/or treatment-experience, was provided mainly by a phase II study, which had limited sample sizes. In the phase II SURVEYOR-2 study 16-week glecaprevir-pibrentasvir (which is licensed regimen for treatment-experienced GT3 patients with and without cirrhosis) was associated with high SVR rates (96% and 94%, respectively) although sample sizes were small: 22 treatment-experienced patients without cirrhosis and 51 treatment-experienced patients with compensated cirrhosis.[2]

The ENDURANCE-3 study provided a direct comparison with sofosbuvir plus daclatasvir in treatment-naïve non-cirrhotic patients with GT3 chronic HCV infection. (N.B. in patients with GT3 daclatasvir is only recommended by SMC in combination with sofosbuvir plus ribavirin for non-cirrhotic patients with significant fibrosis [F3-F4]). There were no direct comparative data relative to relevant comparators in other subgroups defined by genotype, cirrhosis status and previous treatment.

The economic analysis was supported by naïve indirect comparisons. Relevant comparators for GT1 to 3 were identified from the national guideline and for GT4 to 6 appropriate comparators were identified with respect to current SMC guidance. For regimens containing DAA data were derived generally from phase III studies supporting the marketing authorisations. However, data for the peg-interferon plus ribavirin regimen were from only one of several available studies. The usual limitations of naïve indirect comparisons apply, including differences across the studies in design and populations. For both glecaprevir-pibrentasvir and comparators SVR estimates for some cohorts were associated with much uncertainty due to small sample sizes and there were some issues with external validity, e.g. surrounding the SVR for peg-interferon plus ribavirin and the SVR for sofosbuvir plus ribavirin.

The ENDURANCE, EXPEDITION and SURVEYOR studies were not designed to provide data on one-year relapse rates or long-term clinical outcomes. The open-label design of many of the studies may have limited assessment of subjective outcomes, such as quality-of-life or adverse events. Patients with HBV infection were excluded from the glecaprevir-pibrentasvir studies and this limits application of both efficacy and safety data in these groups.

Clinical experts consulted by SMC considered glacaprevir-pibrentasvir to be a therapeutic advancement on the basis that it is a pan-genotypic option that has been shown to be equally

effective regardless of genotype and cirrhotic state, and can also be used in patients with severe renal impairment. They highlighted how its introduction into clinical practice could simplify treatment to a single shorter regimen (8 weeks versus 12 weeks) for all patients and potentially remove the requirement for genotyping in treatment naïve patients, thus providing the opportunity for a move to community-based treatment in primary care outwith the specialist viral hepatitis service.

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

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing glecaprevir-pibrentasvir (GCV/PBV) to relevant comparator treatments in patients with HCV genotypes 1 to 6. The analysis was presented according to a patient's previous treatment experience, eligibility for interferon-based treatment and cirrhosis status. Clinical experts consulted by SMC indicated that grazoprevir-elbasvir is viewed as a relevant comparator for GT1 and GT4, pegylated interferon plus ribavirin for GT2 patients who are eligible for peginterferon, and sofosbuvir-velpatasvir for GT3. The comparators considered for each grouping are shown in the table below:

Table 3: Comparator treatments used in the economic evaluation

Patient group	Comparators considered
Genotype 1	Grazoprevir-elbasvir (GZV/EBV)
Genotype 2	Pegylated interferon plus ribavirin (IFN/RBV) Sofosbuvir plus ribavirin (SOF/RBV)
Genotype 3	Sofosbuvir-velpatasvir (SOF/VEL)
Genotype 4	Grazoprevir-elbasvir (GZV/EBV)
Genotypes 5 and 6	Sofosbuvir plus pegylated interferon plus ribavirin (SOF/IFN/RBV)

A lifetime Markov state transition model was used for the various analyses. The model consisted of two phases. In the first treatment phase, patients were stratified by fibrosis severity and distinct SVR rates were applied from clinical studies to estimate the proportion of patients achieving SVR. Patients then moved to the second, post-treatment, phase that simulated natural disease progression and captured long-term outcomes over the patients' lives. This post-treatment phase included health states for SVR, compensated and decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death. The model structure differentiated between mild and moderate disease among non-cirrhotic patients. Treatment-naive patients were assumed to be aged 43 at the start of the model and treatment-experienced patients were assumed to be aged 45. The proportion of men was 66% and 71%, respectively.

The key clinical variable driving the model was the SVR. For glecaprevir-pibrentasvir, these data were taken from the pivotal ENDURANCE, EXPEDITION and SURVEYOR studies. For the comparator treatments, data were taken from naïve indirect comparisons. Patients who achieved an SVR but started in the cirrhotic state were still exposed to a risk of moving to the decompensated cirrhotic state or the hepatocellular carcinoma state.

For later transitions through the health states in the model, transition probabilities were taken from published literature and largely consistent with values used in other health technology assessments.

Utility values on treatment were estimated from literature sources for all states of the model. For example, a non-cirrhotic patient was assumed to have a base line quality of life score of 0.77, and achieving an SVR increased quality of life by 0.05, which is common to other health technology assessments of hepatitis C treatments. Quality of life while on treatment was also taken into account and it differed among regimens in relation to safety profiles of specific combinations.

Health state costs were largely taken from published sources and similar to health state costs used in other economic models.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. A PAS discount is in place for grazoprevir-elbasvir and this was included in the results used for decision-making by the New Drugs Committee (NDC) by using estimates of the comparator PAS prices. The base case results using an incremental analysis are presented in table 4 below.

Table 4: Cost-effectiveness results

Genotype	Subgroup	Comparator	Incremental cost effectiveness ratios (ICERs) using list prices
GT1	TN NC	GZV/EBV	Dominant (GCV/PBV cheaper, more effective)
	TN CC	GZV/EBV	£12,927
	TE NC	GZV/EBV	Dominant
	TE CC	GZV/EBV	£26,599
GT2 IE	TN NC	IFN/RBV	£36,968
	TN CC	IFN/RBV	£21,738
GT2 II	TN NC	SOF/RBV	Dominant
	TN CC	SOF/RBV	£2,384
GT2	TE NC	SOF/RBV	Dominant
	TE CC	SOF/RBV	Dominant
GT3	TN NC	SOF/VEL	Less effective, less costly
	TN CC	SOF/VEL	Dominant
	TE NC	SOF/VEL	£76,896
	TE CC	SOF/VEL	£92,344
GT4	TN NC	GZV/EBV	Less effective, less costly
	TN CC	GZV/EBV	£383,715
	TE NC	GZV/EBV	Dominant
	TE CC	GZV/EBV	Dominant
GT5	TN NC	SOF/IFN/RBV	Dominant
	TN CC	SOF/IFN/RBV	Dominant
	TE NC	SOF/IFN/RBV	Dominant
	TE CC	SOF/IFN/RBV	Dominant
GT6	TN NC	SOF/IFN/RBV	Less effective, less costly
	TN CC	SOF/IFN/RBV	Dominant
	TE NC	SOF/IFN/RBV	Dominant
	TE CC	SOF/IFN/RBV	Dominant

GT: genotype, TN: treatment-naïve, TE: treatment-experienced, NC: non-cirrhotic, CC: compensated cirrhosis, IE: interferon-eligible, II: interferon-ineligible
GCV/PBV: glecaprevir-pibrentasvir (8-16 weeks)
GZV/EBV: grazoprevir-elbasvir (12 weeks),
SOF/IFN/RBV: sofosbuvir + pegylated interferon + ribavirin (12 weeks)
SOF/RBV: sofosbuvir + ribavirin (12 weeks)
SOF/VEL: sofosbuvir + velpatasvir (12 weeks)
IFN/RBV: pegylated interferon + ribavirin (24 weeks)

For genotype 1 and 4 patients, the results presented in table 4 do not take account of the PAS for grazoprevir-elbasvir or the PAS for glecaprevir-pibrentasvir but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for grazoprevir-elbasvir due to commercial confidentiality and competition law issues. Additionally, SMC would wish to present the glecaprevir-pibrentasvir -PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the glecaprevir-pibrentasvir PAS, SMC is unable to publish these results. As such, only the results without the glecaprevir-pibrentasvir PAS figures can be presented.

The submitting company provided one-way deterministic sensitivity analysis for each subgroup which included most of the input variables. The analysis was most sensitive to changes of utility value for an SVR state and to changes of SVR as a consequence of very close efficacy results and incremental gains in comparison with other DAAs or peginterferon plus ribavirin in GT2 patients. This phenomenon has been seen in previous submissions in HCV.

There are a number of issues with the analyses presented:

- The analysis was driven by naive indirect comparisons for all genotypes, and as such there is uncertainty associated with the relative efficacy of the new regimen compared to existing treatments. The results were very sensitive to any variation of SVR. The gain of outcomes was rather small and uncertain in many subgroups and the incremental costs might be considered as if they were results of a CMA.
- The analysis for GT4, 5 and 6 was based on data from a small number of patients due to low prevalence of these genotypes in Scotland and Europe. This has been a general issue in all GT4-6 HCV submissions. Additional sensitivity analyses provided by the company explored the key uncertainties surrounding SVR rates in these subgroups represented by GT5 cirrhotic patients. Increasing SVR rates to a similar level observed in GT1-3 patients had only a small effect on results.
- The efficacy of peg-interferon plus ribavirin in GT2 patients was based on one of many studies for this combination. However, the effect of SVR that corresponded to the 90% SVR estimation for peg-interferon plus ribavirin noted in the National Guidelines for HCV was tested in sensitivity analysis and this increased the ICERs.

Despite the weaknesses noted, the economic case has been demonstrated.

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

Summary of patient and carer involvement

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

- We received patient group submissions from Waverley Care, The Hepatitis C Trust and Hepatitis Scotland, all three are registered charities.

- Waverley Care has received 1.7% pharmaceutical company funding in the past two years, including from the submitting company. The Hepatitis C Trust has received 50% pharmaceutical company funding in the past two years, including from the submitting company. Hepatitis Scotland has received <1% pharmaceutical company funding in the past two years, with none from the submitting company.

- Hepatitis C is a blood-borne virus that predominantly infects liver cells. This can result in inflammation and significant damage to the liver. The resultant damage to the liver means that people living with the disease can be seriously debilitated. It is a significantly stigmatised disease that can affect employability. All these factors mean that diagnosis can have a devastating impact on the patient, their family and carers.

- Hepatitis C is curable but therapies vary in effectiveness and tolerability. Current treatment regimens range between 12 and 24 weeks, and interferon-containing treatment regimens in particular have significant side effects. Not all patients can tolerate them.

- Glecaprevir/pibrentasvir offers an effective treatment for Hepatitis C. It is an oral regimen with a shorter treatment time and a tolerable side-effect profile. There is less need for frequent hospital visits and a reduced number of blood tests during treatment, which enables more patients to be treated without any significant disruption to their working and family lives.

Additional information: guidelines and protocols

In January 2017 Healthcare Improvement Scotland (HIS) and NHS National Services Scotland published National Clinical Guidelines for the treatment of HCV in adults, version 3.0. Treatment recommendations are presented according to genotype of HCV, which is an important determinant of choice of regimen and chance of cure. The following table summarises treatment regimens by disease classification:[23]

Classification	Recommended regimen
Genotype 1	
Treatment-naïve non-cirrhotic	ombitasvir, paritaprevir, ritonavir, dasabuvir +/- ribavirin (12 weeks) sofosbuvir, ledipasvir (eight weeks) sofosbuvir, simeprevir (12 weeks) sofosbuvir, daclatasvir (12 weeks) (F3-F4 only) elbasvir, grazoprevir (12 weeks)*
Treatment-experienced non-cirrhotic	ombitasvir, paritaprevir, ritonavir, dasabuvir +/- ribavirin (12 weeks) sofosbuvir, ledipasvir (12 weeks) sofosbuvir, daclatasvir (12 weeks) (F3-F4 only) elbasvir, grazoprevir (12 weeks)*
Cirrhotic irrespective of previous treatment	ombitasvir, paritaprevir, ritonavir, dasabuvir + ribavirin (12 weeks) sofosbuvir, ledipasvir + ribavirin (12 weeks) sofosbuvir, daclatasvir + ribavirin (12 weeks) elbasvir, grazoprevir +ribavirin (12 weeks)*
Genotype 2	
Interferon-eligible	peg-interferon alpha +ribavirin (16-24 weeks)
Interferon ineligible or treatment-experienced	sofosbuvir + ribavirin (12 weeks)
Genotype 3	
Non-cirrhotic	Sofosbuvir, velpatasvir (12 weeks) peg-interferon alpha +ribavirin (16-24 weeks) in F0-F1 sofosbuvir, daclatasvir + ribavirin (12 weeks) in F3 only
Cirrhotic	Sofosbuvir, velpatasvir ± ribavirin (12 weeks) sofosbuvir, ledipasvir + ribavirin (12 weeks) sofosbuvir, daclatasvir + ribavirin (12 weeks)
Genotype 4, 5 and 6	
All patients	Genotypes 4, 5 and 6 are uncommon in Scotland. Treatments should be prescribed according to local protocols or where appropriate, expert advice sought.

* In HCV genotype 1a elbasvir grazoprevir for 16 weeks plus ribavirin should be considered in patients with baseline HCV RNA level >800,000 IU/mL and/or the presence of specific NS5A polymorphisms.

Additional information: comparators

In practice the main comparator appears to be elbasvir-grazoprevir in GT1 infection, with other DAA regimens as alternative options. The main comparators in GT2 infection are peg-interferon alpha plus ribavirin for treatment-naïve interferon-eligible patients and sofosbuvir plus ribavirin for treatment-experienced patients or treatment-naïve interferon-ineligible patients. The main comparator in GT3 is sofosbuvir-velpatasvir ± ribavirin. Several regimens containing DAA are treatment options for GT4, 5 and 6 infection.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per course (£)
glecaprevir-pibrentasvir	**Three tablets daily for 8 to 16 weeks**	**25,987 to 51,975**
Daclatasvir Sofosbuvir Ribavirin	60mg orally once daily for 12 weeks 400mg orally once daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	60,304 to 60,465
Daclatasvir Sofosbuvir	60mg orally once daily for 12 weeks 400mg orally once daily for 12 weeks	59,501
Sofosbuvir Simeprevir	400mg orally once daily for 12 weeks One tablet daily for 12 weeks	57,381
Elbasvir-grazoprevir Ribavirin	One tablet daily for 16 weeks 1,000 to 1,200mg daily for 16 weeks	49,738 to 49,952
Ledipasvir-sofosbuvir Ribavirin	One tablet daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	39,784 to 39,944
Sofosbuvir-velpatasvir Ribavirin	One tablet daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	39,784 to 39,944
Ledipasvir-sofosbuvir	One tablet daily for 12 weeks	38,980
Sofosbuvir-velpatasvir	One tablet daily for 12 weeks	38,980
Elbasvir-grazoprevir	One tablet daily for 12 weeks	36,500
Ombitasvir-paritaprevir-ritonavir Dasabuvir Ribavirin	Two tablets once daily for 12 weeks One tablet twice daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	35,804 to 35,965
Sofosbuvir Ribavirin	400mg orally once daily for 12 weeks 1,000 to 1,200mg daily for 12 weeks	35,786 to 35,947
Ombitasvir-paritaprevir-ritonavir Dasabuvir	Two tablets once daily for 12 weeks One tablet twice daily for 12 weeks	35,000
Ledipasvir-sofosbuvir	One tablet daily for 8 weeks	25,987
Peg-interferon-alpha-2b (ViraferonPeg) Ribavirin	1.5mcg/kg once weekly for 16 to 24 weeks 800 to 1,200mg daily for 16 to 24 weeks	3,198 to 4,797*
Peg-interferon-alpha-2a Ribavirin	180mcg once weekly for 16 to 24 weeks 800 to 1,200mg daily for 16 to 24 weeks	2,848 to 4,914

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 July 2017, with the exception of glecaprevir-pibrentasvir (cost taken from submission). Dose regimens are from the national guideline and choice depends on disease classification, (see table in the Additional information: guidelines and protocols section above). Costs do not take any patient access schemes into consideration. costs for both peg-interferon-alpha-2b and ribavirin based on 70kg body weight; SPC for ViraferonPeg notes that the dose for someone weighing 65 to 75kg is 100mcg once weekly combined with ribavirin 1,000mg daily.*

Additional information: budget impact

The submitting company estimated there would be 1,800 patients eligible for treatment with glecaprevir/pibrentasvir in all years. The estimated uptake rate was 100% in year 1 (1,800 patients).

SMC is unable to publish the with- PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

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This assessment is based on data submitted by the applicant company up to and including 15 September 2017**.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.