Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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simeprevir 150mg hard capsules (Olysio ®) SMC No. (988/14)

Janssen

08 August 2014

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

simeprevir (Olysio®) is accepted for use within NHS Scotland.

Indication under review: in combination with other medicinal products for the treatment of chronic hepatitis C in adult patients.

In four double-blind phase III studies, when given as part of triple regimen in combination with peginterferon-alfa and ribavirin, simeprevir was superior to placebo in treatment naive and prior relapsed patients and non-inferior to another direct acting antiviral drug in treatment experienced patients with genotype 1 hepatitis C virus.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Simeprevir is to be used in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adult patients.

Dosing Information

Treatment with simeprevir should be initiated and monitored by a physician experienced in the management of CHC.

The recommended dosage of simeprevir is 150mg capsule once daily for 12 weeks, taken with food. Simeprevir must not be administered as monotherapy. For treatment-naïve and prior relapse patients, peginterferon alfa and ribavirin is administered for 24 weeks and for prior non-responder patients (including partial and null responders), peginterferon alfa and ribavirin is administered for 48 weeks. When considering simeprevir combination treatment with peginterferon alfa and ribavirin in HCV genotype 1a patients, patients should be tested for the presence of virus with the NS3 Q80K polymorphism before starting treatment.

In patients with HCV genotype 1 or 4, regardless of prior treatment history who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment, simeprevir may be administered with sofosbuvir (± ribavirin) for 12 weeks.

Refer to summary of product characteristics (SPC) for further detail including treatment stopping rules in patients with inadequate on-treatment virologic response.

Product availability date

26 May 2014

Summary of evidence on comparative efficacy

Simeprevir is a specific inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease.[1] It can be used to treat genotypes 1 and 4 HCV and must be given in combination with other treatments. It is the fourth direct acting antiviral drug marketed in the UK for chronic hepatitis C (CHC); telaprevir and boceprevir are indicated for treatment of genotype 1 HCV, while sofosbuvir is indicated for treatment of genotypes 1 to 6 HCV.[3-5] All have been accepted for use or restricted use by SMC.

Three phase III, double-blind, placebo-controlled studies have been conducted in adult patients with treatment naive (QUEST 1 and QUEST 2) or prior relapse (PROMISE) genotype 1 HCV.[2,6-12] In the PROMISE study, patients had to have relapsed after ≥24 weeks of interferon based therapy, defined as undetectable HCV RNA at end of treatment (EOT) or within two months after EOT, with documented relapse within one year after therapy. Patients co-infected with human immunodeficiency type 1 (HIV-1) and hepatitis B and with decompensated liver disease were excluded. In all studies, patients were randomised in a 2:1 ratio, with stratification factors (HCV genotype/subtype [1a, 1b, other] and IL28B genotype [CC, CT, TT]), to simeprevir 150mg orally once daily or placebo for 12 weeks. All patients also received PR: peginterferon alfa-2a 180 micrograms/week subcutaneous (sc) injection plus ribavirin 1,000 or 1,200mg/day orally depending on body weight (or peginterferon alfa-2b dose based on weight plus ribavirin 800 to 1,400mg/day in 31% of patients in QUEST 2). PR was administered for 48 weeks, or 24 weeks for patients in the simeprevir group if response guided treatment (RGT) criteria were met: HCV RNA <25 IU/mL at week 4 and undetectable at week 12.

Furthermore, for all patients simeprevir/placebo was stopped if HCV RNA >1000 IU/mL at week 4 and PR was stopped if HCV RNA <2log$_{10}$ IU/mL reduction at week 12 or confirmed ≥25 IU/mL at week 24 or 36.

The primary endpoint in all three studies was sustained virological response at 12 weeks (SVR12) defined as the proportion of patients achieving SVR (HCV RNA <25 IU/mL undetectable) at EOT and HCV RNA <25 IU/mL detectable or undetectable at 12 weeks after planned EOT. In all studies, significantly more patients in the simeprevir than placebo group achieved SVR12 (all p<0.001). Subgroup analysis of SVR12 (baseline HCV RNA, gender, HCV genotype, IL28b and METAVIR score) showed significant differences for simeprevir compared to placebo for all subgroups, except for patients with genotype 1a Q80K at baseline in QUEST 1 and PROMISE. Results of the primary and key secondary endpoints are included in table 1.

Table 1: Results of primary and key secondary endpoints in studies QUEST, QUEST 2 and PROMISE [2,6-12]

	Study					
	QUEST 1		**QUEST 2**		**PROMISE**	
	Simeprevir	**Placebo**	**Simeprevir**	**Placebo**	**Simeprevir**	**Placebo**
N	264	130	257	134	260	133
Primary endpoint						
SVR12; % (n/N)	80% (210/264)	50% (65/130)	81% (209/257)	50% (67/134)	79% (206/260)	36% (48/133)
Difference, 95% CI	29.3%, 20.1 to 38.6		32.2%, 23.3 to 41.2		43.8%, 34.6 to 53.0	
Secondary endpoints						
RGT criteria met; % (n/N)	85% (224/264)	-	81% (235/257)	-	93% (241/260)	-
RVR; % (n/N)	80% (202/254)	12% (15/127)	79% (202/255)	13% (17/133)	77% (200/259)	3.1% (4/129)
On-treatment failure; % (n/N)	9.1% (24/264)	34% (44/134)	7.0% (18/257)	32% (43/134)	3.1% (8/260)	27% (36/133)
Viral relapse; % (n/N)	9.0% (21/234)	21% (18/84)	13% (30/236)	24% (21/88)	18% (46/249)	48% (45/93)

CI=confidence interval, RGT=response guided treatment, RVR=rapid virological response.
RVR was defined as HCV RNA <25 IU/mL undetectable at week 4.
On-treatment failure was defined as HCV RNA confirmed detectable at the EOT.
Viral relapse was defined as detectable HCV RNA among patients with undetectable HCV RNA at EOT.

In a randomised, double-blind, phase III non-inferiority study (ATTAIN), treatment experienced patients with genotype 1 HCV (who were null or partial responders to at least one previous course of PR) were randomised to simeprevir 150mg orally once daily (n=379) or telaprevir 750mg orally three times daily (n=384) for 12 weeks, both in combination with PR (doses as before) for 48 weeks.[7,13] All treatments were stopped if, at week 4 or 12, HCV RNA levels >1000IU/mL or, at week 24 and 36, there was confirmed detectable HCV RNA level. The primary endpoint was SVR12 at EOT, using a non-inferiority margin of 12%. SVR12 was achieved in 54% (203/379) versus 55% (210/384) of patients in the simeprevir and telaprevir groups respectively: difference -1.1 (95% CI: -7.8 to 5.5), non-inferiority was demonstrated. On-treatment virological failure (defined as confirmed HCV RNA levels at EOT) occurred in 34% of simeprevir and 32% of telaprevir-treated patients, and viral relapse in 17% of patients in both groups.

In an open-label study (C212), patients with genotype 1 HCV co-infected with human immunodeficiency type 1 (HIV-1) were treated with simeprevir 150mg orally once daily for 12 weeks plus PR for 48 weeks (24 weeks in non-cirrhotic, treatment-naïve patients or prior relapsers if RGT criteria were met).[1,7,14] The primary endpoint of SVR12 was achieved by 74% (78/106) of the full patient population: 79% in treatment naive group, 87% of relapsers, 70% of partial responders and 57% of null responders.

The efficacy of simeprevir in genotype 4 HCV has been assessed in the on-going open-label RESTORE study.[15,16] All patients were treated with simeprevir 150mg orally once daily for 12 weeks plus PR (doses as before) for 48 weeks (24 weeks in treatment naive or relapser patients if RGT criteria were met). A total of 107 patients have been recruited to the study: 35 treatment naive patients and 72 treatment experienced patients (prior relapsers [n=22], prior partial responders [n=10] and prior null responders [n=40]). At the time-point for the primary endpoint (when all patients reached week 60), 75 patients had completed the study and 29 were still enrolled in the study. The primary endpoint was SVR12 analysed in the ITT population and was achieved in 65% (70/107) of patients. Due to major protocol deviations (>10% of patients), the primary endpoint was also analysed in the per protocol population, and of the 90 evaluable patients, 64% achieved SVR12.

Efficacy of a peginterferon-free regimen was evaluated in the COSMOS study, a randomised phase lla study conducted in two cohorts of patients with genotype 1 HCV.[17,18] Cohort 1 included prior null responders with METAVIR fibrosis score F0 to F2 (n=80), and cohort 2 included treatment-naïve and prior null responder patients with METAVIR fibrosis score F3/ F4 and compensated liver disease (n=87). Patients in both cohorts were randomly assigned to oral treatment with simeprevir 150mg once daily + sofosbuvir 400mg once daily ± ribavarin 1,000 to 1,200mg/day for either 12 or 24 weeks. Stratification was by HCV genotype/subtype and IL28B genotype in cohort 1, and by HCV genotype/subtype and population (naïve/null) in cohort 2. SVR12 was achieved in 93% to 96% of patients treated with for simeprevir + sofosbuvir ± ribavarin for 12 weeks (licensed dose regimen).

Summary of evidence on comparative safety

Pooled safety analysis of QUEST 1, QUEST 2 and PROMISE included 781 patients in the simeprevir group and 397 patients in the placebo group.[6] Discontinuation of simeprevir or placebo due to an AE occurred in 1.8% (14/781) of patients in the simeprevir group and 1.3% (5/397) of patients in the placebo group. Treatment emergent adverse events (AE) of grade 2 to 4 severity and occurring in ≥5% of patients in either group are included in table 2, below.

Table 2: treatment emergent AE (grade 2 to 4 and reported in ≥5% of patients in either group) in pooled analysis of QUEST 1, QUEST 2 and PROMISE studies[6]

	Simeprevir	Placebo
N	**781**	**397**
Neutropenia	12%	11%
Influenza like illness	7.4%	4.0%
Anaemia	6.7%	6.3%
Headache	6.7%	7.3%
Fatigue	6.0%	8.6%
Rash	5.5%	2.5%
Insomnia	5.2%	4.5%
Pyrexia	4.2%	5.3%

The only treatment emergent AE of grade 3/4 (occurring in ≥2% of patients in either group) was neutropenia, occurring in 9.2% versus 8.6% of patients in the simeprevir and placebo groups respectively. The proportion of patients with a serious adverse event was 2.0% (16/781) in the simeprevir group and 2.5% (10/397) in the placebo group.

In the first 12 weeks the most common AE (occurring in ≥25% of either group) included pruritus (31% versus 43%), fatigue (32% versus 38%), headache (25% versus 29%), anaemia (13% versus 37%) and nausea (17% versus 28%), in the simeprevir and telaprevir groups respectively.[13]

The European Medicines Agency (EMA) noted that, overall, simeprevir was well tolerated when added to PR, with very few patients discontinuing due to AEs or suffering serious AEs during treatment.[2]

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

Summary of clinical effectiveness issues

UK and International guidance recommends the use of triple therapy (a direct acting antiviral plus PR) for genotype 1 HCV.[19-21] Simeprevir is the fourth direct acting antiviral drug marketed in the UK for CHC. Telaprevir and boceprevir are indicated for treatment of genotype 1 HCV, while sofosbuvir is indicated for treatment of genotypes 1 to 6 HCV.[3-5] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely treatments with fewer side effects that are better tolerated. Regimens and treatment durations vary across genotypic subgroups for the relevant comparators and also vary depending on previous treatment and response to it, as well as whether RGT is permitted. This produces a complex range of comparative treatment options. Simeprevir for 12 weeks is used in addition to 24 to 48 weeks treatment with PR. Whilst RGT was used in the three pivotal studies (QUEST 1, QUEST 2 and PROMISE), the licensed dose regimen is for fixed durations of PR based on previous treatment.

SVR12 has been accepted by European and US regulators as an appropriate primary endpoint in clinical studies of treatments for CHC.[22] In the placebo-controlled studies conducted in patients infected with genotype 1 HCV, the proportion of patients achieving SVR12 was significantly higher for simeprevir versus placebo (both in addition to PR for 24 to 48 weeks) for treatment naive, prior relapsers and null and partial responders. In addition the non-inferiority of simeprevir + PR versus telaprevir + PR was demonstrated in a patient population that included null and partial responders. Simeprevir was superior to placebo in all subgroup analyses except for patients with genotype 1a Q80K at baseline, in two studies. Efficacy data in patients with genotype 4 HCV are limited to an on-going single-arm study.

In the study investigating peginterferon-free regimens (COSMOS), the addition of ribavirin to the simeprevir + sofosbuvir combination did not appear to contribute to higher SVR rates. However, since the available evidence is limited, the EMA considered that ribavirin could be added to the treatment combination based on a clinical assessment of each individual patient.[2] Also the EMA decided that, due to absence of phase III data, the use of the peginterferon-free regimen should be restricted to patients intolerant to or ineligible for peginterferon therapy.[2]

There are no direct comparative data for simeprevir-containing regimens with current standard triple regimens, except versus telaprevir + PR from the ATTAIN study. As a result of the limited comparative data, the submitting company performed two network meta-analyses (NMA) in treatment naive (8 studies) and treatment experienced (7 studies) patients with genotype 1 HCV. Comparators included telaprevir + PR, boceprevir + PR and PR alone. The efficacy outcome was SVR12 (or 24) and a number of safety outcomes were also analysed. For the genotype 4 HCV population, a

matching-adjusted indirect comparison (MAIC) analysis was undertaken to compare simeprevir + PR with PR alone for SVR12/24. This approach was required as simeprevir efficacy is limited to a single-arm study and therefore a conventional indirect treatment comparison was not possible. Individual patient data from the RESTORE study were matched to the baseline aggregate statistics reported from a study of PR (identified through eligibility matching based on the results of a systematic review).

For the NMA and MAIC analysis, sofosbuvir was not included as a comparator although it has only recently gained marketing authorisation and had SMC advice issued. A recently published frequentist NMA, using a random effects approach, has been conducted in treatment naive and experienced genotype 1 HCV patients treated with triple regimens.[23] The treatment naïve NMA has some limitations including lack of control arms for three of the four sofosbuvir studies, which required the existence of control arms to be assumed for the analysis. For treatment naive patients, the proportion of patients achieving SVR12 was similar for simeprevir + PR (84%, 95% CI 78% to 88%) and sofosbuvir + PR (83%, 95% CI 79% to 87%) and less for boceprevir + PR (73%, 95% CI 68% to 77%) and telaprevir + PR (74%, (95% CI 69% to 79%). Due to lack of data, no comparison was possible with sofosbuvir in treatment experienced patients. The peginterferon-free regimen of simeprevir with sofosbuvir ± ribavirin has not been compared directly or indirectly with the only licensed comparator regimen (sofosbuvir + ribavirin).

Clinical experts consulted by SMC considered that the place in therapy of simeprevir is as an alternative to other protease inhibitors plus peginterferon/ribavirin regimens. Simeprevir (and sofosbuvir) are administered as one tablet daily compared to telaprevir (six tablets) and boceprevir (12 tablets). Testing for the presence of the Q80K polymorphism in patients with HCV genotype 1a should be peformed before starting simeprevir and alternative therapy should be considered when Q80K polymorphism is detected, or in cases where testing is not accessible.[1] Telaprevir, boceprevir and sofosbuvir do not have such restrictions. The estimated prevalence of HCV genotype 1a with Q80K polymorphism in Europe is 19%.[24] The SPC includes stopping rules for simeprevir: at week 4 if HCV RNA ≥ 25 IU/ml then simeprevir, peginterferon and ribavirin should be stopped; and at week 12 or 24 if HCV RNA is detectable then PR should be stopped. Stopping rules also apply for telaprevir and boceprevir.

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

Summary of comparative health economic evidence

The submitting company presented lifetime cost-utility analyses comparing simeprevir in triple or dual therapy in three patient HCV sub-populations according to genotype and suitability for interferon treatment. Analysis for genotype 1 patients who were negative for the Q80K polymorphism consisted of a comparison of simeprevir + PR with telaprevir + PR, boceprevir + PR and PR alone. Analysis for genotype 4 patients compared simeprevir + PR versus PR alone. The third sub-population analysis was for HCV patients with genotype 1 who were intolerant or ineligible for interferon therapy and in urgent need for treatment (i.e. fibrosis score of F3-F4), which involved comparison of simeprevir + sofosbuvir against simeprevir + PR, telaprevir + PR, boceprevir + PR and PR alone. The most relevant comparators for genotype 1 patients are the protease inhibitor + PR regimens, as confirmed by SMC clinical experts. However, the comparators for the genotype 1 intolerant or ineligible for interferon therapy population are not appropriate as they all contain pegylated interferon.

For each sub-population analysis, a common Markov modelling structure based on existing published models was used. The model consisted of an on-treatment decision tree with SVR according to fibrosis score as the outcome, and a long term Markov model with disease progression health states covering mild and moderate HCV, compensated cirrhosis, decompensated cirrhosis, hepatocellular

carcinoma, liver transplant, post liver transplant and liver related death. Patients were assumed to have a starting age of 41 years in the model.

The clinical data on SVR rates, disease severity and prior treatment experience characteristics for each sub-population analysis were drawn from various sources. The primary source of clinical data for the genotype 1 sub-population was the NMA, which included a non-inferiority trial of simeprevir + PR versus telaprevir + PR in treatment experienced patients. For the genotype 4 sub-population, data were drawn from the MAIC of a single arm simeprevir + PR trial (RESTORE) with a single PR trial in treatment naive patients, and for the genotype 1 intolerant or ineligible for interferon therapy population, a naïve indirect comparison was performed including the COSMOS study for the simeprevir/sofosbuvir combination. Clinical data from these sources were not always available for each drug regimen to fully populate the economic model for each analysis (e.g. SVR by fibrosis score, or by treatment naïve versus treatment experienced patients); in these cases, assumptions were made based on data that were available or based on clinical expert opinion. Extrapolation from SVR to disease progression health states was taken from published economic evaluations in HCV that had previously been used in health technology assessments (HTAs) of HCV therapies.

On-treatment utility decrements for simeprevir + PR and the comparator regimens for the genotype 1 and 4 patient populations were based on EQ-5D values collected in clinical trials, with the simeprevir + PR regimens generally having lower or similar decrements relative to the comparators. There was a lack of on-treatment utility data for the simeprevir/sofosbuvir combination in treatment naïve and null responders, hence EQ-5D values for the naïve and null responders to simeprevir + PR in genotype 1 patients were applied. Base case utility values by fibrosis score (0.77 for F0-F2, 0.66 for F3, 0.55 for F4) were drawn from the published UK Mild HCV infection study, and a utility increment of 0.05 applied for patients experiencing an SVR based on a published study. Utilities for disease progression health states were those used in previous HTAs of HCV infection drugs, with a value of 0.45 applied for decompensated cirrhosis, hepatocellular carcinoma and liver transplant states.

The standard treatment duration associated with each regimen was assumed to vary across sub-populations. In each sub-population for treatment naïve patients and in treatment experienced prior relapsers, the duration of simeprevir + PR and telaprevir + PR was 12 weeks followed by 12 weeks PR alone (hence PR for 24 weeks). In treatment experienced prior non-responders, 48 weeks of PR was assumed. A longer duration of boceprevir + PR of 24 weeks and 32 weeks was assumed in treatment naïve and treatment experienced prior relapsers respectively, and 48 weeks in total of PR in treatment experienced prior non-responders. Both telaprevir and boceprevir + PR regimens could have the possibility of longer treatment durations in treatment naïve (both regimens) or prior relapser patients (only telaprevir + PR) if HCV infection remained detectable. In all patients the PR regimen alone consisted of 48 weeks of PR. The regimens used were stated to be the recommended durations in the respective summary of product characteristics (SPC). In assessing drug related costs, account was taken of Q80K polymorphism testing costs for simeprevir and RGT rules for dose adjustment and duration of PR therapy that apply to telaprevir and boceprevir regimens. SPC defined stopping rules according to HCV RNA levels during treatment were applied for all the protease inhibitors. Monitoring costs for each regimen and costs for management of key adverse events were included, and non-treatment specific health state costs were derived from a published report on HCV infection.

The base case results for each sub-population by treatment naïve and experienced patient populations are presented in the tables below.

Genotype 1 sub-population

	Simeprevir + PR Incremental cost	Simeprevir + PR Incremental quality adjusted life year (QALY)	Incremental cost-effectiveness ratio (ICER) simeprevir+PR vs. comparators
Treatment naïve: ICER Simeprevir + PR vs. comparators			
PR	£9,562	0.875	£10,922
Telaprevir + PR	-£4,545	0.121	Dominant
Boceprevir + PR	-£2,750	0.192	Dominant
Treatment experienced: ICER Simeprevir+ PR vs. comparators			
PR	£7,049	1.261	£5,591
Telaprevir + PR	-£1,731	0.076	Dominant
Boceprevir + PR	-£7,478	0.237	Dominant

Genotype 4 sub-population

	Simeprevir +PR Incremental cost	Simeprevir +PR Incremental QALY	Simeprevir +PR ICER vs. PR
Treatment naive ICER vs.			
PR	£11,460	0.773	£14,824
Treatment experienced ICER vs.			
PR	£10,425	1.255	£8,304

Genotype 1 intolerant or ineligible for interferon therapy (F3-F4)

	Simeprevir + sofosbuvir Incremental cost	Simeprevir + sofosbuvir Incremental QALY	ICER of simeprevir + sofosbuvir vs. comparator
Treatment naive ICERs vs comparators			
Simeprevir + PR	£18,878	1.084	£17,416
Telaprevir+PR	£13,967	1.329	£10,511
Boceprevir + PR	£4,417	2.019	£2,187
PR	£23,426	2.273	£10,305
Treatment experienced ICERs vs comparators			
Simeprevir+sofosbuvir			
Simeprevir + PR	£7,194	2.319	£3,102
Telaprevir+PR	-£1,278	2.499	Dominant
Boceprevir + PR	-£5,622	2.093	Dominant
PR	£13,898	3.351	£4,147

In the genotype 1 sub-population, cost savings compared to telaprevir + PR, and boceprevir + PR regimens were due to shorter durations of treatment for simeprevir + PR resulting in lower drug costs, and QALY gains from a lower incidence of clinical events and liver related deaths. There were higher drug costs associated with the simeprevir/sofosbuvir combination relative to the comparators, but relatively high QALY gains predicted, especially in treatment experienced patients. Sensitivity and scenario analysis in genotype 1 patients indicated some sensitivity to uncertainty regarding relative SVR outcomes, and relaxing an assumption that patients with an SVR and fibrosis score of F0-F3 do not progress to DCC, although simeprevir + PR remained dominant vs. telaprevir or boceprevir + PR. There was higher sensitivity to variation in some parameters for the genotype 4 sub-population analysis such that allowing patients with SVR to have a probability of progression to decompensated cirrhosis and hepatocellular carcinoma increased the ICER versus PR alone to £18k/QALY and £44k/QALY in treatment naïve and experienced patients respectively. In the genotype 1 patients intolerant or ineligible for interferon therapy, the most sensitive variable was varying the SVR

probability, although an upper limit of £25.7k/QALY versus simeprevir + PR, in treatment naïve patients, but none of the other ICERs exceeded £20k/QALY in either treatment naïve or experienced patients.

The main issues with the economic analyses in each sub-population relates to the clinical evidence base and comparators used as follows:

- For genotype 1, there are some limitations in the data available from the NMA for populating the on-treatment part of the economic model. The main issue relates to the estimated differences in SVR versus boceprevir + PR that are used in the model as it is likely to include differences that may not be statistically significant in the NMA. The company subsequently provided results including only statistically significant differences from the NMA. This did not impact significantly on the results for treatment naïve patients. In treatment experienced patients there were no significant efficacy differences observed versus telaprevir or boceprevir + PR from the NMA, hence any QALY gains estimated for simeprevir are uncertain. However, cost savings are still expected for simeprevir + PR over the alternative protease inhibitors + PR due to the expected shorter treatment duration of the former.
- For genotype 4 patients there are limited clinical data for the MAIC of simeprevir versus PR alone, so there are greater uncertainties associated with the relative SVR efficacy estimates. The MAIC that has been performed for treatment naïve patients is based on very limited patient numbers, with potential bias associated with the single study selected for the comparator PR regimen. In addition, a MAIC could not be performed for genotype 4 treatment experienced patients, so the results for the NMA for the genotype 1 sub-population were instead used to provide proxy SVR values. The limitations of the indirect comparisons in genotype 4 patients have partly been addressed by the current sensitivity/scenario analysis which indicates a good probability that the ICER versus PR will be under £20k/QALY especially in treatment experienced patients (although there are a few scenarios in which the ICER exceeds £30k/QALY). Further scenario analyses were requested from the company including using alternative PR studies for SVR rate of the comparator. The data available for the MAIC from these studies were extremely limited, although the ICERs estimated remained within boundaries of acceptable cost-effectiveness.
- In genotype 1 patients intolerant or ineligible for interferon therapy, there are concerns that the comparators to interferon-free simeprevir/sofosbuvir are inappropriate as they all include PEG-IFN therapy. It would be more appropriate to have comparisons with sofosbuvir plus ribavirin (the only other licensed treatment for these patients) or with no treatment. In addition, the clinical evidence used has limitations, with the SVR outcome data having been drawn from a naïve indirect comparison with uncertain study selection criteria. Hence, there is high uncertainty in the cost-effectiveness results produced against the comparators that were considered. The company provided a subsequent comparison against 'no treatment', assuming an SVR rate of 0% for this comparator, estimating ICERs of £7,622 and £7,018 per QALY gained for simeprevir/sofosbuvir in treatment naïve and experienced patients respectively. Sensitivity analysis was also provided around these estimates and this indicated that the cost per QALY ratios remained below £20,000 when key parameters were varied.
- In the genotype 1 and 4 sub-populations, comparisons were not originally performed versus sofosbuvir regimens, which SMC clinical experts have indicated as being potentially displaced in due course. Although the company has subsequently provided some indicative analyses for this comparison across patient sub-populations, this has not been considered here given the timing of the SMC decision for sofosbuvir.
- Cost-effectiveness of simeprevir in patients co-infected with HIV has not been fully assessed, although the company presented data in genotype 1 patients to suggest cost-effectiveness would not be expected to differ from that observed for the whole genotype 1 population.

Despite some limitations, particularly in the clinical data and indirect comparisons performed, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specific patient group.

- A submission was received from the Hepatitis C Trust, which is a registered charity.
- The Hepatitis C Trust has received funding from several pharmaceutical companies in the past two years, including from the submitting company.
- Hepatitis C is a blood-borne virus that can result in inflammation and significant damage to the liver, affecting its ability to perform essential functions. The hepatitis C virus (HCV) can affect a number of other areas of the body including the digestive, lymphatic and immune systems, and the brain.
- People living with the disease can be seriously debilitated and may be unable to work; some have lost their jobs when they have revealed their HCV status. Living with HCV is often a challenge which impacts on family, carers and the patient.
- Current treatments can be lengthy with challenging side effects. Simeprevir addresses an unmet need for patients who are intolerant of current treatments and for patients with genotype 4.
- Simeprevir can have a reduced treatment duration, potentially improved side-effect profile and may be better tolerated. This may encourage more people to be tested, diagnosed and successfully treated.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) guideline number 133, management of hepatitis C, was published in July 2013.[19] The following recommendations are included:

- Treatment-naïve and treatment-experienced patients infected with hepatitis C genotype 1 should be considered for treatment with pegylated interferon and weight based ribavirin with the addition of a protease inhibitor as triple therapy.
    - Response-guided therapy can only be used in treatment-naïve patients and previous treatment relapsers who are not cirrhotic.
- For patients with hepatitis C genotype 4 (and 5 or 6) infection, standard treatment should be 48 weeks of pegylated interferon and weight based ribavirin.
- Patients co-infected with HIV and hepatitis C genotype 1 should be considered for treatment with a regimen that includes a hepatitis C virus protease inhibitor.
    - Treatment-naïve patients with HIV and hepatitis C genotype 1 who are unsuitable for this regimen should be considered for treatment with pegylated interferon and weight based ribavirin for 48 to 72 weeks depending on viral response.
    - For patients co-infected with HIV and hepatitis C genotype 1 who do not achieve an early virological response, treatment should be stopped.
    - Patients with HIV and hepatitis C non-genotype 1 who are considered suitable for treatment, should be offered pegylated interferon and weight-based ribavirin for 48 weeks.

Patients co-infected with hepatitis B and C should be considered for treatment with pegylated interferon and weight-based ribavirin.

The European Association for Study of the Liver (EASL) published EASL Clinical Practice Guidelines: Management of hepatitis C virus infection in 2014.[20] The guidelines includes the following recommendations:

Genotype 1

- The combination of PR and telaprevir or boceprevir is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of telaprevir or boceprevir as preferred therapy
- Patients with cirrhosis should never receive abbreviated treatment in boceprevir or telaprevir treatment regimens
- Selected patients with high likelihood of SVR to PR or with contraindications to boceprevir or telaprevir can be treated with dual therapy
- When lead-in is used to identify patients with interferon-α- sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment
- Both pegylated interferon-α molecules, peginterferon-α 2a(180microgram/week) and peginterferon-α 2b (1.5microgram/kg/week), can be used in dual or triple therapy
- Ribavirin should be dosed following the pegintereron-α label for triple therapy
- Ribavirin should be given at a weight-based dose of 15mg/kg in dual therapy

Genotype 2, 3, 4, 5 and 6 treatment naive patients

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

The guidelines predate the licensing of simeprevir (and sofosbuvir).

The World Health Organisation (WHO) published Guidelines for the screening, care and treatment of persons with hepatitis C infection in April 2014.[21]
The guidelines include the following recommendations for treatment:

- Pegylated interferon in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-pegylated interferon with ribavirin.
- Treatment with telaprevir or boceprevir, given in combination with pegylated interferon and ribavirin, is suggested for genotype 1 chronic hepatitis C infection rather than pegylated interferon and ribavirin alone.
- Sofosbuvir, given in combination with ribavirin with or without pegylated interferon (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than pegylated interferon and ribavirin alone (or no treatment for persons who cannot tolerate interferon).
- Simeprevir, given in combination with pegylated interferon and ribavirin, is recommended for persons with HCV genotype 1b infection and for persons with HCV genotype 1a infection without the Q80K polymorphism rather than pegylated interferon and ribavirin.

Additional information: comparators

The standard treatment for genotype 1 HCV is peginterferon and weight-based ribavirin plus a telaprevir, boceprevir or sofosbuvir with RGT determining treatment duration in certain groups (24 to 48 weeks). For patients with genotype 4, standard treatment is with PR ± sofusbuvir. The only peginterferon-free comparator regimen is sofosbuvir plus ribavirin.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Simeprevir Peginterferon-alfa-2a Ribavirin	**150mg daily for 12 weeks 180mcg once weekly for 24 to 48 weeks 1000mg to 1200mg daily for 24 to 48 weeks**	**27,222 to 32,058**
Simeprevir* Sofosbuvir ±ribavirin	**150mg daily for 12 weeks 400mg once daily for 12 weeks ±1000mg to 1200mg daily for 12 weeks**	**57,369 to 58,294**
Sofosbuvir Peginterferon-alfa-2a Ribavirin	400mg once daily for 12 to 24 weeks 180mcg once weekly for 12 to 24 weeks 1000mg to 1200mg daily for 12 to 24 weeks	37,400 to 74,801
Sofosbuvir** Ribavirin	400mg once daily for 24 weeks 1000mg to 1200mg daily for 24 weeks	71,816
Boceprevir*** Peginterferon-alfa-2b Ribavirin	800mg three times daily for 24 to 48 weeks 1.5mcg/kg once weekly for 28 to 48 weeks 800mg to 1800mg for 28 to 48 weeks	22,397 to 43,194
Telaprevir*** Peginterferon-alfa-2a Ribavirin	2250mg daily in divided doses for 12 weeks 180mcg once weekly for 24 to 48 weeks 1000mg to 1200mg daily for 24 to 48 weeks	27,234 to 32,069
Peginterferon-alfa-2a Ribavirin	180mcg once weekly for 24 to 48 weeks 1000mg to 1200mg daily for 24 to 48 weeks	4,836 to 9,672
Peginterferon-alfa-2b Ribavirin	1.5mcg/kg once weekly for 24 to 48 weeks 800mg to 1800mg daily for 24 to 48 weeks	4,797 to 9,594

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis on 21 May 2014 (based on a body weight of 70kg), MIMS and company's submission (for simeprevir). The Copegus® brand of ribavirin is indicated for use in combination with peginterferon-alfa-2a and the Rebetol® brand of ribavirin is indicated for use in combination with peginterferon-alfa-2b. Peginterferon-alfa-2a was generally used in the pivotal studies of simeprevir and it is included in the other regimens for consistency. It is combined with ribavirin (Copegus®), weight based dosing of 1000mg if body weight <75kg and 1200mg, if body weight >75kg. An alternative treatment option is peginterferon-alfa-2b at a dose of 1.5microgram per kg once weekly, combined with ribavirin (Rebetol®) at a daily dose of 800mg, 1000mg, 1200mg or 1800mg, if body weight <65kg, 65-80kg, 81-105kg or >105kg, respectively.

* only suitable in patients who are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment (ribavirin could be added based on a clinical assessment of each individual patient); **only suitable for patients who are intolerant of or ineligible for treatment with peginterferon; ***licensed for use in genotype 1 HCV only

Additional information: budget impact

For the genotype 1 sub-population, the submitting company estimated there to be 572 patients eligible for treatment with simeprevir + PR in year 1 rising to 588 in year 5, with an estimated uptake rate of 31% in year 1 (177 patients) and 55% in year 5 (324 patients). These figures were arrived at assuming that only 6% of hepatitis C patients are treated. The submitting company estimated the gross medicines budget impact to be £4.8m in year 1 and £8.8m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be savings of £431k in year 1 and £779k in year 5. The displaced medicines cost related to a mix of telaprevir and boceprevir regimens.

For the genotype 4 sub-population, the the submitting company estimated there to be 37 patients eligible for treatment with simeprevir + PR in year 1 rising to 38 in year 5, with an estimated uptake rate of 25% in year 1 (9 patients) and 60% in year 5 (23 patients). The submitting company estimated the gross medicines budget impact to be £245k in year 1 and £603k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £148k in year 1 and £365k in year 5.

For the genotype 1 sub-population intolerant or ineligible for interferon therapy and in urgent need of treatment, the submitting company estimated there to be 50 patients eligible for treatment with simeprevir + sofosbuvir in year 1 rising to 48 in year 5, with an estimated uptake rate of 34% in year 1 (17 patients) and 59% in year 5 (29 patients). The submitting company estimated the gross medicines budget impact to be £975k in year 1 and £1.64m in year 5. As no other medicines were assumed to be displaced, the net medicines budget impact was estimated the same as the gross.

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The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 10 July 2014.

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

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

Advice context:

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

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