ombitasvir 12.5mg / paritaprevir 75mg / ritonavir 50mg (Viekirax®) film-coated tablet and dasabuvir 250mg (Exviera®) film-coated tablet.

SMC No. (1051/15)

AbbVie

08 May 2015

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

**ADVICE**: following a full submission

This document includes advice on two products; ombitasvir/paritaprevir/ritonavir (Viekirax®) and dasabuvir (Exviera®).

**ombitasvir/paritaprevir/ritonavir (Viekirax®)** is accepted for use within NHS Scotland.

**dasabuvir (Exviera®)** is accepted for use within NHS Scotland.

**Indications under review:**

- Ombitasvir/paritaprevir/ritonavir (Viekirax®) for use in combination with dasabuvir (Exviera®) with or without ribavirin for the treatment of genotype 1 chronic hepatitis C (CHC) in adults

- Ombitasvir/paritaprevir/ritonavir (Viekirax®) for use in combination with ribavirin for the treatment of genotype 4 CHC in adults

In six phase III studies, conducted in patients with genotype 1 CHC, rates of sustained virological response at 12 weeks post-treatment were achieved in ≥96% of patients who received licensed treatment regimens of ombitasvir/paritaprevir/ritonavir + dasabuvir, irrespective of sub-genotype, previous treatment and presence of cirrhosis.

Overleaf is the detailed advice on these products.

**Chairman, Scottish Medicines Consortium**
Indications
- Ombitasvir/paritaprevir/ritonavir (Viekirax®) for use in combination with dasabuvir (Exviera®) with or without ribavirin for the treatment of genotype 1 CHC in adults
- Ombitasvir/paritaprevir/ritonavir (Viekirax®) for use in combination with ribavirin for the treatment of genotype 4 CHC in adults

Dosing Information
Treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir should be initiated and monitored by a physician experienced in the management of CHC.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1b without cirrhosis</td>
<td>ombitasvir/paritaprevir/ritonavir, two tablets once daily plus dasabuvir one tablet twice daily</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1b with compensated cirrhosis</td>
<td>ombitasvir/paritaprevir/ritonavir, two tablets once daily plus dasabuvir one tablet twice daily plus ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a without cirrhosis</td>
<td>ombitasvir/paritaprevir/ritonavir, two tablets once daily plus dasabuvir one tablet twice daily plus ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a with compensated cirrhosis</td>
<td>ombitasvir/paritaprevir/ritonavir, two tablets once daily plus dasabuvir one tablet twice daily plus ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Genotype 4 without cirrhosis</td>
<td>ombitasvir/paritaprevir/ritonavir, two tablets once daily plus ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4 with compensated cirrhosis</td>
<td>ombitasvir/paritaprevir/ritonavir, two tablets once daily plus ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Refer to ribavirin Summary of Product Characteristics for relevant dosing details.

Product availability date
Ombitasvir/paritaprevir/ritonavir: January 2015.
Dasabuvir: January 2015.

Summary of evidence on comparative efficacy
This document includes advice on two products; ombitasvir/paritaprevir/ritonavir (Viekirax®) and dasabuvir (Exviera®) when taken as part of a combination antiviral drug regimen. Ombitasvir/paritaprevir/ritonavir (Viekirax®) is a combination tablet containing ombitasvir (an inhibitor of hepatitis C virus [HCV] NS5A), paritaprevir (an inhibitor of HCV NS3/4A protease) and ritonavir (a CYP3A inhibitor that increases the systemic exposure of the CYP3A substrate paritaprevir and is not active against HCV). Dasabuvir (Exviera®) is a non-nucleoside inhibitor of the HCV RNA polymerase encoded by the NS5B gene. In genotype 1 CHC, ombitasvir/paritaprevir/ritonavir plus dasabuvir provides treatment with three direct-acting antiviral agents with differing mechanisms of action and resistance profiles which target HCV at multiple steps in the viral lifecycle. In patients with genotype 4 CHC,
ombitasvir/paritaprevir/ritonavir is indicated and contains two direct-acting antiviral agents. In all patients co-administration with ribavirin is required, except those with non-cirrhotic genotype 1b CHC.\textsuperscript{1,2}

Efficacy data come from six multi-centre, randomised, controlled phase III studies conducted in patients aged 18 to 70 years with genotype 1 CHC and an HCV RNA level of $>10,000$ IU/mL and one phase II study (PEARL-I) in patients with genotype 4 CHC.\textsuperscript{1-8}

SAPPHIRE-I and -II were placebo-controlled (for safety comparisons only) studies in non-cirrhotic patients with genotype 1 CHC who were treatment-naive (SAPPHIRE-I) or treatment-experienced (SAPPHIRE-II). Patients were randomised to treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin or placebo for 12 weeks. TURQUOISE-II was an open-label study in treatment-naive and treatment-experienced patients with genotype 1 CHC and compensated cirrhosis. Patients were randomised to treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin for 12 or 24 weeks. PEARL-II was an open-label study in non-cirrhotic, treatment-experienced patients with genotype 1b CHC. Patients were randomised to 12 weeks treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin for 12 or 24 weeks. PEARL-III and -IV were double-blind studies in non-cirrhotic, treatment-naive patients with genotype 1b CHC (PEARL-III) and genotype 1a (PEARL-IV). Patients were randomised to 12 weeks treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin or ombitasvir/paritaprevir/ritonavir + dasabuvir + placebo. In studies of treatment-naive patients, randomisation was stratified according to interleukin 28B genotype and in studies of treatment-experienced patients, randomisation was stratified according to previous response. In SAPPHIRE-I and -II and TURQUOISE-II, randomisation was also stratified according to sub-genotype. Patients who were treatment-experienced were required to have had a relapse, a partial response or null response to peginterferon + ribavirin for study entry. Some studies included treatment regimens which do not have marketing authorisation; these are indicated in the results table.\textsuperscript{3-7}

The primary endpoint for all studies was sustained virological response at 12 weeks post treatment (SVR12), defined as HCV RNA level $<25$ IU/mL at 12 weeks after the end of treatment. All studies assessed the non-inferiority of treatment regimens to historical control rates (based on treatment with telaprevir plus peginterferon + ribavirin) which were weighted according to sub-genotype, whether patients had cirrhosis, and were treatment-naive or experienced according to the population for each study. In all studies, the non-inferiority and superiority of treatment regimen(s) versus the historical control rate was demonstrated (see table 1; NB only the treatment regimens which are shaded are licensed). Comparisons between treatment regimens were also performed for TURQUOISE-II and PEARL-II, -III and -IV studies as secondary analyses. In PEARL-IV, the proportion of patients with SVR12 was significantly higher for the ribavirin-containing treatment regimen compared to the treatment regimen without ribavirin.\textsuperscript{3-7}
Table 1: SVR12 results for phase III studies conducted in patients with genotype 1 CHC (shaded regimens are licensed)³-⁷,⁹

<table>
<thead>
<tr>
<th>Treatment regimen 1</th>
<th>Treatment regimen 2</th>
<th>Historical control rate</th>
<th>Difference between treatment regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12 % (n/N), (CI)</td>
<td>SVR12 % (n/N), (CI)</td>
<td>(CI)</td>
<td>(CI)</td>
</tr>
<tr>
<td>SAPPHIRE-I: genotype 1, treatment-naive, non-cirrhotic.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + ribavirin (12 weeks)</td>
<td>96% (455/473), (95% CI: 94.5 to 97.9)</td>
<td>not applicable</td>
<td>78% (95% CI: 75 to 80)</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 94.5 to 97.9)</td>
<td>not applicable</td>
<td>not applicable</td>
</tr>
<tr>
<td>SAPPHIRE-II: genotype 1, treatment-experienced, non-cirrhotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + ribavirin (12 weeks)</td>
<td>96% (286/297), (95% CI: 94.2 to 98.5)</td>
<td>not applicable</td>
<td>65% (95% CI: 60 to 70)</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 94.2 to 98.5)</td>
<td>not applicable</td>
<td>not applicable</td>
</tr>
<tr>
<td>TURQUOISE-II: genotype 1, treatment-naive and -experienced, compensated cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + ribavirin (12 weeks)</td>
<td>92% (191/208), (97.5% CI: 87.6 to 96.1)</td>
<td>not applicable</td>
<td>47% (95% CI: 41 to 54)</td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + ribavirin (24 weeks)</td>
<td>96% (165/172), (97.5% CI: 92.6 to 99.3)</td>
<td>CiC*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(97.5% CI: 92.6 to 99.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEARL-II: genotype 1b, treatment-experienced, non-cirrhotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + ribavirin (12 weeks)</td>
<td>97% (85/88), (95% CI: 92.8 to 100)</td>
<td>not applicable</td>
<td>69% (95% CI: 62 to 75)</td>
</tr>
<tr>
<td>Viekirax® + dasabuvir (12 weeks)</td>
<td>100% (91/91), (95% CI: 95.9 to 100)</td>
<td>CiC*</td>
<td>3.4% (95% CI: -0.4 to 7.2)</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 95.9 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEARL-III: genotype 1b, treatment-naive, non-cirrhotic.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + ribavirin (12 weeks)</td>
<td>99% (209/210), (95% CI: 98.6 to 100)</td>
<td>not applicable</td>
<td>80% (95% CI: 75 to 84)</td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + placebo (12 weeks)</td>
<td>99% (207/209), (95% CI: 97.7 to 100)</td>
<td>CiC*</td>
<td>-0.5% (95% CI: -2.1 to 1.1)</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 97.7 to 100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEARL-IV: genotype 1a, treatment-naive, non-cirrhotic.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + ribavirin (12 weeks)</td>
<td>97% (97/100), (95% CI: 93.7 to 100)</td>
<td>not applicable</td>
<td>72% (95% CI: 68 to 75)</td>
</tr>
<tr>
<td>Viekirax® + dasabuvir + placebo (12 weeks)</td>
<td>90% (185/205), (95% CI: 86.2 to 94.3)</td>
<td>CiC*</td>
<td>-6.8% (95% CI: -12.0 to -1.5)</td>
</tr>
<tr>
<td></td>
<td>(95% CI: 86.2 to 94.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=number with SVR12, N=number of patients in ITT population, CI=confidence interval.
* treatment regimen is not licensed. Historical control rate was based on treatment with telaprevir plus peginterferon + ribavirin and weighted according to sub-genotype, whether patients had cirrhosis, were treatment-naive or -experienced according to the population for each study.

Secondary endpoints included virological failure during treatment and virological relapse post treatment. Virological failure during treatment was defined as a confirmed HCV RNA level of ≥25 IU/mL after the HCV RNA level had been <25 IU/mL during treatment, or a confirmed increase in the HCV RNA level of >1 log₁₀ IU/mL above the nadir observed during treatment, or if all the HCV RNA values during the treatment with the study drug administered for ≥6 weeks were ≥25IU/mL. Across the studies virological failure on treatment occurred in 0% to 1.7% of patients who received licensed treatment regimens. Virological relapse post treatment was defined as a confirmed HCV RNA level of ≥25 IU/mL between the final treatment visit and 12 weeks after receipt of the last dose of study drug among patients who completed treatment, who
had an HCV RNA level that was <25 IU/mL at the final treatment visit during the double-blind period, and who had HCV RNA data available after treatment. Across the studies, virological relapse occurred in 0% to 2.4% of patients who received licensed treatment regimens.\textsuperscript{3-7}

Three instruments were used to assess health related quality of life: short-form 36 version 2 (SF-36v2), EuroQol 5 dimensions (EQ-5D) and HCV patient reported outcomes (HCV-PRO) total score. For the SF-36 physical component summary and mental component summary scores, the minimally important difference (MID) was defined as -5 units. For the HCV-PRO total score and the EQ-5D-5L Health Index Score, the MID was defined by receiver operating characteristic analysis using the SF-36v2 mental component summary and physical component summary MIDs of -5 as anchor scores. The majority of patients (in most of the studies) did not report decreases from baseline to end of treatment period ≥MID in health related quality of life using these instruments.\textsuperscript{9-14}

PEARL-I was a phase II study in patients aged 18 to 70 years with genotype 1b or genotype 4 CHC. The treatment arms that included patients with genotype 1b CHC are not reported here as they did not use licensed treatment regimens. Results for patients with genotype 4 CHC are presented. Patients with genotype 4 CHC were required to be treatment-naïve, or treatment-experienced (as for SAPPHIRE-II study), have HCV RNA level >10,000 IU/mL at screening and be non-cirrhotic for ≥6 months prior to screening. Treatment-naïve genotype 4 CHC patients were randomised equally, stratified by IL28B genotype (CC versus non-CC), to 12 weeks treatment with ombitasvir/paritaprevir/ritonavir (group 1 [unlicensed treatment regimen]) or ombitasvir/paritaprevir/ritonavir + ribavirin (group 4). Treatment-experienced genotype 4 CHC patients received 12 weeks treatment with ombitasvir/paritaprevir/ritonavir + ribavirin (group 6). SVR12 was achieved in 91% (40/44) of patients in group 1, 100% (42/42) of patients in group 4 and 100% (49/49) of patients treated in group 6. There was one virological failure and two virological relapses (all in group 1).\textsuperscript{1,8}

TURQUOISE-I is an on-going open-label phase III study in genotype 1 CHC patients co-infected with HIV-1. Patients were required to be on a stable HIV-1 antiretroviral therapy regimen that included ritonavir-boosted atazanavir or raltegravir, co-administered with a backbone of tenofovir plus emtricitabine or lamivudine. Patients were randomised to 12- or 24-weeks’ treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin. SVR12 rates are available for 63 patients who have completed the study. SVR12 was achieved in 94% (29/31) (95% CI: 79.3 to 98.2) of patients who received 12 weeks treatment and 91% (29/32) (95%CI: 75.8 to 96.8) of patients who received 24 weeks treatment. There was one virological relapse in the 12-week group and one virological failure and two virological relapses in the 24-week group.\textsuperscript{1,8}

CORAL-I is an on-going, phase II, open-label study conducted in adult liver transplant patients with genotype 1 CHC. In cohort 1, patients with fibrosis ≤ F2 were enrolled and had not received treatment for HCV infection after transplantation. They received 24-weeks treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin. SVR12 rates are available for 34 patients (29 with HCV genotype 1a infection and 5 with HCV genotype 1b infection) who have completed the study. SVR12 was achieved in 97% of patients with genotype 1a CHC and 100% of patients with genotype 1b CHC. One patient (with genotype 1a CHC) had a virological relapse.\textsuperscript{1,15}

*Other data were also assessed but remain commercially confidential*
Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summaries of product characteristics for details.\(^1,2\)

The most common treatment emergent adverse events included fatigue, headache, nausea, pruritus, insomnia, diarrhoea, asthenia and dyspnoea.\(^1,7\)

The safety of ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin in patients with compensated cirrhosis was similar to patients without cirrhosis except for increased rates of transient hyperbilirubinemia.\(^1\)

In PEARL-II, -III and -IV the decrease in haemoglobin level from baseline to the end of treatment to less than the lower limit of normal (LLN) occurred in a significantly higher proportion of patients treated with the regimen that included ribavirin than without ribavirin. Ribavirin-containing regimens are not used for genotype 1b non-cirrhotic patients. Also, in PEARL-I and -II the proportion of patients with total bilirubin increase to >3 times upper limit of normal was significantly higher for patients treated with the regimen that included ribavirin than without ribavirin.\(^5,7\)

Summary of clinical effectiveness issues

Ombitasvir/paritaprevir/ritonavir is licensed for use in combination with dasabuvir ± ribavirin in patients with genotype 1 CHC. Ombitasvir/paritaprevir/ritonavir is licensed for use in combination with ribavirin in patients with genotype 4 CHC. Four other peginterferon-free treatments have recently been licensed for CHC. While regimens containing sofosbuvir (plus ribavirin) and simeprevir (plus sofosbuvir ± ribavirin) are only used in patients ineligible or intolerant to peginterferon alfa (and urgent need of treatment [simeprevir]) the daclatasvir (plus sofosbuvir ± ribavirin) and ledipasvir/sofosbuvir ± ribavirin peginterferon-free regimens do not have such restrictions. Other relevant comparators are regimens containing peginterferon + ribavirin.\(^1,2,16-19\) Treatment of CHC is changing rapidly and there is currently no clear guidance on a treatment pathway that incorporates these recently-licensed treatments.

Ombitasvir/paritaprevir/ritonavir in combination with dasabuvir is the first treatment regimen licensed in the UK that includes a NS5A protein inhibitor, NS3/4A protease inhibitor and a NS5B polymerase inhibitor. Currently licensed regimens of direct-acting antiviral agents (DAA) include a NS5B polymerase inhibitor (sofosbuvir) in combination with either a NS5A protein inhibitor (ledipasvir or daclatasvir); a NS3/4 protease inhibitor (simeprevir) ± ribavirin; and ribavirin alone.

In the phase III studies conducted in patients with genotype 1 CHC, SVR12 rates were achieved in ≥96% of patients who received licensed treatment regimens, irrespective of sub-genotype, previous treatment and presence of cirrhosis. These high response rates are likely to be clinically significant. In all studies the non-inferiority and superiority of treatment regimens containing ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin versus the historical control rates was demonstrated for SVR12, which has been accepted as a valid endpoint by the European Medicines Agency.\(^20\). Furthermore rates of virological failure on treatment and virological relapse post treatment were low.\(^3-7\)
There are limited efficacy data in patients with genotype 4 CHC from the phase II study, and no efficacy data in cirrhotic patients with genotype 4 CHC. However, the EMA has noted in its assessment that, as regimens with 2 direct acting antiviral agents 2DAA were highly effective when given for 24 weeks to cirrhotic patients with HCV GT1b, it appears that an inference of likely similar efficacy can be made for regimens with 2DAA plus ribavirin if given for 24 weeks to cirrhotic patients with HCV GT4. In Scotland, of the people with CHC who had genotype testing, 48% had genotype 1, 46% had genotype 3 and 6% had other genotypes. 

There are no direct comparative efficacy or safety data for ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin to relevant comparators, such as those peginterferon-free regimens containing sofosbuvir, simeprevir, daclatasvir or ledipasvir/sofosbuvir. The submitting company noted that an indirect treatment comparison was not possible due to lack of a control arm in the studies as well as other methodological issues.

Ombitasvir/paritaprevir/ritonavir containing regimens necessitate co-administration with ribavirin, except for treatment-naive non-cirrhotic patients with genotype 1b CHC. There are peginterferon-free and ribavirin-free regimens available e.g. daclatasvir + sofosbuvir and ledipasvir/sofosbuvir can be used in certain patient groups according to licensed indication and SMC restricted advice. In the phase III studies, the addition of ribavirin to ombitasvir/paritaprevir/ritonavir-containing regimens resulted in a significantly higher proportion of patients achieving decreases in haemoglobin <LLN. However, across the studies, decreases in health related quality of life measures ≥ MID were not seen.

In patients with genotype 1 CHC the ombitasvir/paritaprevir/ritonavir + dasabuvir regimen requires that four tablets are taken daily (in addition to ribavirin, when indicated). This compares to one tablet daily for ledipasvir/sofosbuvir and two tablets daily for daclatasvir + sofosbuvir regimen (in addition to ribavirin, when indicated). Any impact for the patient regarding the higher pill burden for the regimen under review compared to these comparator regimens is uncertain. 

**Summary of comparative health economic evidence**

The submitting company presented a lifetime cost-utility analysis of ombitasvir/paritaprevir/ritonavir administered with dasabuvir ± ribavirin (3D regimen) in genotype 1 CHC and ombitasvir/paritaprevir/ritonavir + ribavirin (2D regimen) in genotype 4 CHC patients. The base case genotype 4 analysis was for non-cirrhotic patients only. A range of comparators was used in the analysis, depending on the patients’ eligibility for interferon-based therapy and their previous treatment status:

- For genotype 1, the comparators were sofosbuvir+pegylated interferon+ribavirin (SOF+PR), telaprevir +PR, boceprevir+ PR, no treatment, and PR alone.
- For genotype 4, the comparators were SOF+PR, PR and no treatment.

The analysis was presented for treatment-naive and treatment-experienced subgroups separately.

For each of the scenarios considered, a common Markov model structure was used. This included states for SVR, mild and moderate CHC, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death. In common with other models for CHC, an SVR is assumed to be a cure. At baseline, patients were assumed to be aged 40 for
treatment-naive patients or 45 for treatment-experienced patients, with 10% and 32% assumed to be cirrhotic in each population respectively.

The key clinical data in the model related to the SVR rates from the initial treatment choice, and then patients flowed through the subsequent states of the model according to transition probabilities from published sources. The SVR rates for the 3D and 2D regimens were taken from the clinical trial programmes described above. As there is a lack of directly comparative data against other treatment options, the SVR data for comparators were taken from the respective published papers for each treatment option. As such, the SVR rates were from a naive indirect comparison.

The utility values were taken from a published UK HTA study which used EQ-5D to elicit values in CHC patients. As with previous CHC models, the analysis used a 0.05 gain in quality of life for patients who achieved an SVR. Disutilities while on treatment were also allowed for in the model; these were estimated from EQ-5D data from the key studies for the 3D and 2D regimens and from published papers for comparator treatments.

Health state costs were mainly estimated from published papers, and the medicines cost of the 3D and 2D regimens was estimated directly from usage data in the key studies. Adverse event costs and ongoing monitoring (including for SVR patients) were included.

Using incremental analysis where multiple treatment comparators existed, the results of the analysis were as follows:

<table>
<thead>
<tr>
<th>Genotype 1, treatment-naive, interferon eligible patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>3D regimen versus PR (all other regimens ruled out by dominance principles)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 1, treatment-experienced, interferon eligible patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D regimen versus PR (other regimes ruled out by dominance principles)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 1, treatment-naive, interferon unsuitable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D regimen versus no treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 1, treatment-experienced, interferon unsuitable patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D regimen versus no treatment</td>
</tr>
<tr>
<td>Genotype 4, treatment-experienced, interferon eligible patients (non-cirrhotics only)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>2D regimen versus no treatment</td>
</tr>
</tbody>
</table>

| Genotype 4, treatment-naive, interferon-eligible patients (non-cirrhotics only) |  |
|---|---|---|
| 2D regimen versus PR (other regimens ruled out by dominance principles) | £17,204 | 0.85 | £20,351 |

| Genotype 4, treatment-naive, interferon unsuitable patients (non-cirrhotic) |  |
|---|---|---|
| 2D regimen versus no treatment | £19,260 | 2.53 | £7,614 |

A range of one-way and scenario-based sensitivity analyses were presented around these ICERs. In the one-way analysis, the results showed that the assumed utility value for SVR responders in mild or moderate patients was a key variable in the results. For example, if 20% lower values were assumed, the ICER in the genotype 1, treatment-naive, interferon-eligible group rose to between £25k and £30k per QALY in comparison with telaprevir plus PR, boceprevir plus PR and PR alone. However, it should be noted that the utility gain for responders in the base case was a value commonly used and accepted in CHC modelling. In the pairwise comparison with SOF+PR for genotype 1, treatment-naive, interferon-eligible patients, the results remained dominant (3D cheaper, more effective).

Scenario analysis investigated the impact on the results if a 10% reduction in the SVRs was assumed for the 3D and 2D regimens. The ICERs almost all remained below £20k. However for the genotype 1, treatment-naive, interferon eligible patients, SOF+PR became dominant in the pairwise comparison. The ICER versus PR increased to £17k. For genotype 4, treatment-naive, interferon eligible patients, the ICER versus PR rose to £31,380.

There were a number of issues with the analyses:
- As with other recent new treatments for CHC, a key weakness was the lack of a formal indirect comparison with other relevant treatments. The scenario analysis showing the impact of assuming a 10% reduction in SVR rates was therefore helpful in showing that the ICERs were generally robust and the submitting company indicates that such reductions in efficacy are not likely in practice. A further issue is a lack of clarity on what current treatments are being used given the rapidly changing range of available treatments; this makes it harder to be certain of the relevant comparators for the analyses.
- The analysis above did not include genotype 4 patients with cirrhosis. Following the New Drugs Committee meeting, the submitting company provided some revised analysis to include these patients into the calculations, based on the extrapolation of data from genotype 1b cirrhotic patients. This resulted in relevant ICERs of £20,234 for GT4 treatment-naive IFN eligible patients versus PR and £11,485 for GT4 treatment-experienced IFN eligible patients versus no treatment. Sensitivity analysis around these estimates indicated that the results remained below £30k per QALY when relevant parameters were varied.
- The ongoing monitoring costs for patients who achieve an SVR were relatively modest.
compared to previous submissions. However, the company provided additional analysis to show values more in line with previous submissions; this increased the relevant ICERs in the incremental analysis by around £1,500 to £2,500.

Despite these issues, the economic case has been demonstrated.

Summary of patient and public involvement

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

- Submissions were received from Waverley Care, The Hepatitis C Trust, Hepatitis Scotland and Haemophilia Scotland. All four are registered charities.
- All four charities have received pharmaceutical company funding in the past two years with Waverley Care, The Hepatitis C Trust and Hepatitis Scotland receiving funding 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 it has a devastating impact on the patients, their family and carers.
- Hepatitis C is curable but therapies vary in effectiveness and tolerability. Current treatment regimens are long, and pegylated interferon containing treatment regimens in particular have significant side effects. Not all patients can tolerate them.
- Viekira and Exviera offer an effective treatment for Hepatitis C. As an oral regimen with a shorter treatment time and more tolerable side-effect profile than currently available therapies, it may allow more patients to engage effectively with their treatment regimen and achieve SVR.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guidance number 133; ‘Management of hepatitis C’ in 2006, which was updated in July 2013. Recommendations in relation to the management of CHC include:

- All patients with chronic HCV infection should be considered for antiviral therapy.
- Sustained viral response should be used as a marker for viral clearance.
- All treatment-naive patients infected with HCV genotype 1 should be considered for treatment with pegylated interferon and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.
- All treatment-experienced patients infected with HCV genotype 1 should be considered for treatment with pegylated interferon and weight-based ribavirin with the addition of a protease inhibitor as triple therapy.
- Treatment-naive patients co-infected with HIV and HCV genotype 1 who are unsuitable for treatment with a regimen which includes HCV protease inhibitors should be
considered for treatment with pegylated interferon and weight-based ribavirin for 48-72 weeks depending on viral response.

- In treatment-experienced patients with a lower likelihood of SVR, benefits of treatment need to be weighed against potential risks and side effects.
- Response-guided therapy can only be used in treatment-naive patients and previous treatment relapers who are not cirrhotic.
- 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.
- For patients with HCV genotype 4, 5 or 6 infections, standard treatment should be 48 weeks of pegylated interferon and weight-based ribavirin.

The National Institute for Health and Care Excellence (NICE) published Multiple Technology Appraisal Guidance number 200, ‘Use of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C’ in 2010.\(^2\)\(^3\) It recommends peginterferon alfa (2a or 2b) plus ribavirin as a possible treatment for people with CHC:

- who have been treated previously with peginterferon alfa (2a or 2b) plus ribavirin, or with peginterferon alfa monotherapy, but their hepatitis C didn't improve, or improved but then got worse again
- or who also have an HIV infection.

NICE recommends short courses of treatment with peginterferon alfa (2a or 2b) plus ribavirin for people whose hepatitis C has greatly improved within 4 weeks of starting treatment and who are suitable for short treatment courses.

The British HIV Association published ‘Guidelines for the management of hepatitis viruses in adults infected with HIV’, in 2013.\(^2\)\(^4\) Recommendations include:

- all patients should be managed by a clinician experienced in the management of both HIV and hepatitis C or should be jointly managed by clinicians from HIV and hepatitis backgrounds.
- all patients with HCV/HIV infection should be assessed for suitability for treatment of hepatitis C.

For those with genotype 1, treatment recommendations include:

- where there is a current clinical need for treatment (i.e., METAVIR F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with triple therapy consisting of pegylated interferon, ribavirin, and either telaprevir or boceprevir.
- 48 weeks of total treatment with a telaprevir- or boceprevir-based regimen for patients who do not have cirrhosis.
- all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them.
- a total of 48 weeks of treatment in patients with cirrhosis and for those who do not achieve a rapid virologic response (RVR).
- non-cirrhotic patients who were previously null responders, partial responders or who experienced breakthrough should, wherever possible, wait for the availability of interferon-sparing regimens or interferon based regimens including at least two new agents.
all patients with advanced or decompensated cirrhosis being treated with triple therapy are managed in a tertiary centre.

for patients with genotype 1 infection and non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with hepatic elastography or alternative non-invasive testing at least annually. Where there is confirmed progression of fibrosis, treatment initiation should be reconsidered.

For those with genotype 4, treatment recommendations include:

- for patients with genotype 4 infection without cirrhosis, there is the option to defer treatment until newer therapies or a suitable clinical trial become available.
- if treatment is given now, this should be with pegylated interferon and ribavirin. The duration of therapy should be 48 weeks if RVR is achieved. If the RNA is still detectable at 12 weeks, consideration should be given to discontinuing treatment.
- waiting for the availability of interferon-sparing regimens with active direct acting antivirals in those individuals with previous treatment failure.

The European Association for Study of the Liver (EASL) published ‘EASL Clinical Practice Guidelines: Management of hepatitis C virus infection’, in 2014. 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 peginterferon-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-naïve 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

EASL published ‘EASL recommendations on treatment of hepatitis C’, in April 2014. The guidance provides advice on medicines approved by the European Medicines Agency up to the end of 2014. For genotype 1 or 4 CHC, six treatment options are detailed (see guidance for specific details):

- option 1: peginterferon + ribavirin + sofosbuvir
- option 2: peginterferon + ribavirin + simeprevir
- option 3: peginterferon + ribavirin + daclatasvir
- option 4: ribavirin + sofosbuvir
option 5: sofosbuvir + simeprevir
option 6: sofosbuvir + daclatasvir
The guidelines will be updated as new medicines become available.

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).

### Additional information: comparators

Sofosbuvir, simeprevir, daclatasvir, ledipasvir/sofosbuvir in peginterferon-free regimens. Telaprevir, boceprevir, sofosbuvir, simeprevir and daclatasvir in combination with peginterferon plus ribavirin.

### Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peginterferon-free regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir dasabuvir ribavirin</td>
<td>two tablets once daily 12 to 24 weeks one tablet twice daily 12 to 24 weeks 1,000mg to 1,200mg orally 12 to 24 weeks</td>
<td>35,925 to 71,850</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir dasabuvir*</td>
<td>two tablets once daily 12 weeks one tablet twice daily 12 weeks</td>
<td>35,000</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir ribavirin**</td>
<td>two tablets once daily 12 to 24 weeks 1,000mg to 1,200mg orally 12 to 24 weeks</td>
<td>33,125 to 66,250</td>
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<tr>
<td>ledipasvir/sofosbuvir</td>
<td>90mg/400mg orally once daily for 8 to 24 weeks</td>
<td>24,987 to 77,960</td>
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<tr>
<td>ledipasvir/sofosbuvir ribavirin</td>
<td>90mg/400mg orally once daily for 24 weeks 1,000mg to 1,200mg orally daily for 24 weeks</td>
<td>79,567 to 79,810</td>
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<tr>
<td>Daclatasvir Sofosbuvir ribavirin</td>
<td>60mg orally daily for 12 to 24 weeks 400mg orally daily 12 to 24 weeks</td>
<td>59,502 to 119,004</td>
</tr>
<tr>
<td>Daclatasvir sofosbuvir ribavirin</td>
<td>60mg orally daily for 24 weeks 400mg orally daily for 24 weeks 1,000mg to 1,200mg orally daily for 24 weeks</td>
<td>120,852</td>
</tr>
</tbody>
</table>
Simeprevir
sofosbuvir ± ribavirin
150mg orally daily for 12 weeks
400mg orally daily for 12 weeks
1,000mg to 1,200mg orally daily for 12 weeks
57,381 to 58,306

sofosbuvir ribavirin
400mg orally daily for 24 weeks
1,000mg to 1,200mg orally daily for 24 weeks
71,816

**Peginterferon containing regimens**

daclatasvir peginterferon-alfa-2a ribavirin
60mg orally daily for 24 weeks
180 micrograms sc weekly for 24 to 48 weeks
1,000mg to 1,200mg orally daily for 24 to 48 weeks
53,872 to 58,707

simeprevir peginterferon-alfa-2a ribavirin
150mg orally daily for 12 weeks
180 micrograms sc weekly for 24 to 48 weeks
1,000mg to 1,200mg orally daily for 24 to 48 weeks
27,234 to 32,069

sofosbuvir peginterferon-alfa-2a ribavirin
400mg orally daily for 12 to 24 weeks
180 micrograms sc weekly for 12 to 24 weeks
1,000mg to 1,200mg orally daily for 12 to 24 weeks
37,401 to 74,802

boceprevir peginterferon-alfa-2b ribavirin
800mg three times daily for 24 to 48 weeks
1.5 microgram/kg once weekly for 28 to 48 weeks
800mg to 1,800mg orally daily for 28 to 48 weeks
22,397 to 43,194

telaprevir peginterferon-alfa-2a ribavirin
2250mg daily in divided doses for 12 weeks
180 microgram sc once weekly for 24 to 48 weeks
1,000mg to 1,200mg orally daily for 24 to 48 weeks
27,234 to 32,069

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis (February 2015) and MIMS. Costs are based on a body weight of 70kg (i.e. ribavirin dose of 1,000mg/day). sc=subcutaneously.*genotype 1b non-cirrhotic regimen;**genotype 4 regimen.

Refer to SPCs for detailed information on regimens, duration of treatment and HCV genotype that treatments are used for.

### Additional information: budget impact

The submitting company estimated there to be approximately 16,000 patients with chronic hepatitis C (Genotype 1 only) in Scotland. The company estimated that treatment uptake would be 6% in year 1, rising to 9% by year 5. With a discontinuation rate of 1.56% per year, this resulted in patient numbers of 427 in year 1, rising to 650 by year 5.

The submitting company estimated the gross medicines budget impact to be £16.8m in year 1 and £25.7m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of £334k in year 1, rising to a saving of £524k in year 5. These estimates assumed that two-thirds of patients would be treatment-naïve, and one-third treatment-experienced. The displaced medicine was assumed to be sofosbuvir-containing regimens. The magnitude of any cost-savings in clinical practice will therefore depend on the current treatments used. The estimates did not include genotype 4 patients, but this is likely to be a very small patient group.
References

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

8. www.clinicaltrials.gov
9. *Commercial in confidence
10. *Commercial in confidence
11. *Commercial in confidence
12. *Commercial in confidence
13. *Commercial in confidence
14. *Commercial in confidence
http://apps.who.int/iris/bitstream/10665/111747/1/9789241548755_eng.pdf?ua=1&ua=1

This assessment is based on data submitted by the applicant company up to and including 17 April 2015.

*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.