(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☑ No ☐

Please provide brief details:
There are 150 million people chronically infected with hepatitis C worldwide and at least half a million die from hepatitis C related disease yearly. Simeprevir is a once-daily oral second-generation protease inhibitor. Greater treatment responses are possible in comparison to previous Interferon (IFN)/Ribavirin (RBV) based therapy, and the first-generation oral NS3/4A protease inhibitors (i.e., Telaprevir and Boceprevir). Simeprevir in combination with Peg-IFN/RBV or a second directly acting anti-HCV agent offers improved treatment response and shorter treatment durations for many patients afflicted with chronic hepatitis C. Treatment will reduce individual morbidity and mortality as well as the risk of further transmission to uninfected individuals. Access to improved anti-HCV treatment options, especially in resource-limited low-medium income countries, will be an important step to reduce the global burden of chronic hepatitis C.

(2) Have all important studies that you are aware of been included in the application? Please provide brief comments on any relevant studies that have not been included:

Yes ☐ No ☑

Studies not included in the Application:
- Phase 2b ASPIRE – treatment experienced patients with HCV genotype 1 treated with Peg-IFN/RBV/placebo for 48 weeks or Peg-IFN and Simeprevir (100 or 150 mg) for 12, 24 or 48 weeks.
- Sofosbuvir/Simeprevir combination for recurrent HCV post-Liver Transplant (Hepatology Feb 2015)

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☑ No ☐

Briefly summarise the reported outcomes (e.g. clinical, surrogate, other) and comment, where possible, on the magnitude of clinical benefit associated with use of the medicine: The primary end-point is SVR 12 (HCV RNA measured by a highly sensitive assay at 12 weeks post-treatment), showing a high concordance to SVR 24.
Thus SVR 12 is accepted measure indicating successful treatment response – i.e., a functional cure and reduced risk of severe liver disease.

(4) **Is there evidence of efficacy in diverse settings and/or populations?**

Yes [ ] No [x] [ ]

Please provide brief details:
- Efficacy was demonstrated in HCV Genotype 1 and Genotype 4 Infection. Treatment is not recommended for HCV genotype 2 or 3 infection. In Genotype 4 efficacy is poor in prior partial and null responders.
- An important limitation is in patients with genotype 1a infection, testing for a specific HCV genome polymorphism (i.e., q80K) is needed if considering treatment with IFN/RBV/SIM. The q80K or gln80Lys is a naturally occurring mutation in HCV NS3/4A protease and is more prevalent in North American HCV1a strains compared to Europe. If the q80K mutation is present, Simeprevir has no antiviral effect; one should consider alternative treatment options.

**Treatment regimens included**
- All oral (i.e., combination with nucleotide polymerase inhibitor, Sofusbuvir)
- Combination Peg-IFN/RBV/Simeprevir.

**Patient population included:**
- HIV/HCV coinfected
- Cirrhotic (Child-Pugh A only)
- Prior non-responder/relapser
- Adults only

(5) **Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?**

Yes [x] No [ ] [ ]

Please provide brief details:
- Limited data in patients over age 65, and none if over age 75
- Safety in patients not established in severe renal impairment (GFR<30 ml/min), highly protein bound
- Caution when treating patients with Child-Pugh class B or C (not been clinically studied)
- DDI’s with anti-HIV antiretrovirals
- Interactions with other drugs that induce or inhibit cytochrome P4503A
- East Asian populations had higher exposure to the drug and a higher frequency of adverse events compared to other ethnicities. No data on HBV/HCV coinfection
- In the clinical trials adverse events/side effects were mainly due to the effects if Peg-IFN and Ribavirin. In Peg-IFN/RBV/Simeprevir rash, pruritis, photosensitivity and asymptomatic hyperbilirubinemia were more common compared to Peg-IFN/RBV/placebo-treated patients.
- All-oral therapy (Simeprevir and Sofusbuvir) was well tolerated, and low pill burden
60,000 people treated with Simeprevir; post-marketing data showed no unrecognized adverse reaction and safety profile similar to that established in clinical trials.
- The FDA has advised that in patients with moderate or severe hepatic impairment or in East Asians the drug may not be advisable.

ADDITIONAL CONSIDERATIONS:

(6) **Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?**
- Yes ☐
- No ☐

Please provide brief details:
Experience in treatment of chronic hepatitis C, and management of liver disease, especially in cirrhotic patients. The need for testing for the q80K polymorphism in patients with HCV genotype 1a infection (i.e., sequencing analysis) prior to starting simeprevir therapy may limit the drug usage for Peg-IFN/RBV/Simeprevir combination therapy.

(7) **Are there any issues regarding the registration of the medicine by regulatory authorities?** *(e.g., recent registration, new indications, off-label use)*
- Yes ☐
- No ☐

Please provide brief details:
- Data on Simeprevir and Sofosbuvir post-liver transplant recently published.
- The drug has received regulatory approval in 10 countries, and submitted for approval in 22 countries at the time of sponsor application.
- The FDA has advised in patients with moderate or severe hepatic impairment or in East Asian populations, Simeprevir may not be advisable

(8) **Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?**
- Yes ☒
- No ☐

Please provide brief details:
In recent WHO HCV treatment guidelines that Simeprevir + Peg-IFN/RBV was preferred to Peg-IFB/RBV.

(9) **Please comment briefly on issues regarding cost and affordability of this medicine.**
- The sponsor (Janssen pharmaceuticals) indicted that there are no current prices for low-medium income countries but the company is committed to affordable pricing in the setting of countries where HCV is a major public health concern
- Since oral combination therapy is needed for IFN-free regimens, the pricing and access will be affected by cost and availability of Sofosbuvir, which is manufactured by Gilead pharmaceuticals.
Any additional comments?

Limitations include:
- The lack of data in East Asians, decompensated cirrhosis, genotypes 2 and 3
- Drug interactions through metabolism cytochrome p450 3A4 enzyme pathways
- The need for q80K testing if genotype 1a, may limit applicability in combination Peg-IFN/RBV regimens but the effect is attenuated in Simeprevir/Sofusbuvir combination therapy.

On March 23rd, 2015, the United States Prescribing Information for ledipasvir/sofosbuvir (Harvoni) and sofosbuvir (Sovaldi) was updated following reports of serious and life-threatening cases of symptomatic bradycardia following use of amiodarone with either Harvoni (LDV/SOF), or Sovaldi (sofosbuvir, SOF) in combination with another direct acting antiviral (daclatasvir or simeprevir). Thus, coadministration of amiodarone with Sofosbuvir in combination with ledipasvir or another directly acting antiviral agent will no longer be allowed in clinical trials.

Please summarise the action you propose the Expert Committee takes.
- Simeprevir has a number of limitations but inclusion in WHO list of Essential Medicines is recommended, as greater anti-HCV treatment options / choices in the context of a significant public health burden will ultimately improve access and reduce cost (i.e., provide impetus for generic competition)
- Simeprevir in combination with Peg-IFN/RBV should be considered second-line therapy given the safety and efficacy data with all-oral interferon free regimens.