(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. In comparison to previous Interferon (IFN)/Ribavirin (RBV) based therapy, and the first generation oral directly acting antiviral agents (DAA’s), Ledispavir and Sofusbuvir combination is a safe, effective, and well-tolerated treatment 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?  

Yes ☑ No ☐

Please provide brief comments on any relevant studies that have not been included: The major Phase 3 clinical trials (i.e., ION1, ION2, ION3 studies in HCV genotype 1), as well as clinical trials that included Sofusbuvir based therapy were included. The Phase 2 studies included a diverse range of patient populations with HCV genotype 1, 3, 4 and 6 infection. Most recent major guidelines have been updated to recommend Sofusbuvir/Ledispavir for HCV treatment.

(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 main clinical end-point assessed was undetectable HCV RNA indicating a sustained virological response (SVR) at 3 months after the end of treatment (i.e, SVR-12). This surrogate end-point is a well-recognized indicator of successful response to treatment, low risk of virological relapse, and reduced risk of hepatitis C related morbidity and mortality.
(4) **Is there evidence of efficacy in diverse settings and/or populations?**

Yes [X]  No [ ]

**Please provide brief details:** Effectiveness was demonstrated in historically hard to treat populations (i.e., human immunodeficiency virus (HCV) coinfected, HCV recurrence after liver transplant, decompensated cirrhosis, older age, renal impairment, prior treatment failures). Importantly, compared with other anti-HCV directly acting antivirals (DAA’s) there was a low incidence of drug-drug interactions (DDI), with immunosuppressive therapy, and with anti-HIV antiretroviral therapy. Treatment is approved for patients infected with genotype 1, genotype 4, and some genotype 3 patients. The drug has not been tested, and is not recommended for use in paediatric populations or in pregnant or nursing women. The shortened treatment duration and improved tolerability profile will increase patient eligibility for treatment in a wide range of patients.

(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 [ ]  No [X]

**Please provide brief details:** Monitoring requirements are generally less rigorous, compared to interferon based therapies and first generation DAA’s. However in HIV coinfected patients on nucleoside analog (Tenofovir, TDF) the half-life of TDF is increased due to DDI’s, and may require monitoring for TDF associated side effects (i.e., renal dysfunction). Other DDI’s occur with drugs that induce P-glycoprotein. Thus a thorough pharmacy review for potential DDI’s is essential. The overlapping resistance profiles of LDV and SOF are important advantages for this combination therapy. In particular presence of baseline resistant associated variants did not overall impact treatment effectiveness.

**ADDITIONAL CONSIDERATIONS:**

(6) **Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?**

Yes [ ]  No [X]

**Please provide brief details:** Treatment should be under the care of a physician with experience with hepatitis C therapy, and in the case of cirrhotic patients, experience with liver disease management. In particular patient treatment adherence is important, as indicated by the one treatment failure in a patient who was found to have sub-therapeutic antiviral drug plasma levels. Consideration regarding DDI’s with Tenofovir should also be noted.

(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 ☐ X

Please provide brief details: The treatment has been approved by most major expert guidelines.

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

Please provide brief details: Sofosbuvir was added last year

(9) Please comment briefly on issues regarding cost and affordability of this medicine.
The drug is available in developed countries but the cost is prohibitive for many without private drug insurance plans. Further negotiations in resource limited countries for reduced drug prices and improved access to treatment (i.e., similar to HIV antiviral access) are planned.

(10) Any additional comments?
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

(11) Please summarise the action you propose the Expert Committee takes.
Addition to the WHO list of essential medicines