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

Yes [x] 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), second generation DAA’s offers improved treatment responses, shorter treatment duration, and in Interferon-free regimens, reduced side effect profile. Daclatasvir is an inhibitor of the HCV NS5A polymerase. Successful 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 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 [x] No [ ]

Please provide brief comments on any relevant studies that have not been included:

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

Yes [x] 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 (undetectable 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 HCV-related morbidity and mortality.

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

Yes [x] No [ ]

Please provide brief details:
Pangenotype (Genotypes 1-4), effective in cirrhotic, HIV co-infection, previous treatment failures (Peg-IFN/RBV and 1st generation DAA’s), and non-IL28B CC genotype, African Americans

- Most data for treatment of Genotype 3 infection compared to other second generation DAA’s
- Initial studies on Genotype 1b
- Ongoing trials for Genotype 1a

(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: The application suggests all-oral DAA with Daclatasvir in combination with Sofusbufvir. This combination meets the criteria of high efficacy, acceptable safety and pan-genotypic potential. Clinical trials demonstrated safety data. In animals, the only safety concerns are with high doses (i.e., bone marrow hypocellularity in dogs). Other side effects were related to Peg-IFN and RBV (not with DAA’s).

- No difference in cirrhotic vs non-cirrhotics

ADDITIONAL CONSIDERATIONS:

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

Please provide brief details:
- Should be prescribed by specialist in management of HCV and/or HIV co-infection, and in treatment of cirrhotic patients.
- There may be drug-drug interactions with HIV anti-virals.

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

Please provide brief details:

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?
   Yes X No
Please provide brief details: Decompensated liver disease
- Active viral replication with active histological inflammation and/or fibrosis

(9) Please comment briefly on issues regarding cost and affordability of this medicine.
- Since combination therapy is needed, the pricing and access will be affected by cost and availability of Sofusbuvir, which is manufactured by Gilead pharmaceuticals. The data clearly support the use of a second generation DAA as first-line treatment of HCV.
- Greater anti-HCV treatment options / choices in the context of a significant public health burden will ultimately improve access and reduce cost, and increase market pressure for generic formulations

(10) Any additional comments? The drug is approved by major expert guidelines (i.e., EASL) and endorsed by Doctors without borders (MSF).

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.
- Inclusion in WHO list of Essential Medicines