Expert peer review on application for PEG IFN alfa (2a and 2b) for HCV

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes ✔ No (if no, please provide reference and information)

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      Treatment with peginterferon alfa-2a or -2b and ribavirin for 48 weeks has resulted in SVR rates of 45% for genotypes 1 and 4 and for genotypes 2 and 3, 24 weeks of therapy has resulted in 80% SVR rates.

      A recent meta-analysis shows that treatment success rates in low- and middle-income countries were similar to those obtained in high-income countries.

   c. Please provide any additional relevant information with reference

      There is no evidence on long term clinical outcomes such as survival, cirrhosis and cancer.

      The information available for the directness of treatment effectiveness deserves further scrutiny (as shown by the recent introduction of novel therapies for HCV).

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes ✔ No (if no, please provide reference and information)

   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      The most common side effect of interferon which can also be contraindications to treatment, are:
      - severe, flu-like symptoms such as fever, fatigue, and muscle pains in most patients.
      - abnormal blood counts, with patients showing reduced levels of hemoglobin, white cells, and platelets.
      - others: psychological side effects (depression emotional lability), hemolytic anemia and thyroid dysfunctioning.

   c. Please provide any additional relevant information with reference

      About 10-15% of patients suspends the treatment and about a third needs some dose reduction to deal with side effects.
3. **Assessment of cost and availability**
   a. Have all relevant data on safety provided
      Yes ☑ No (if no, please provide reference and information)
      The application was particularly weak on the description of the safety profile. See also Ghany MG et al Diagnosis, Management, and Treatment of Hepatitis C: An Update. Hepatology 2009; 49:4:1335-1374
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      Data on cost were not presented in the application.
   c. Please provide any additional relevant information with reference
   d. Is the product available in several low and middle income countries?
      Generic manufacturers are now available in various countries.

4. **Assessment of public health need**
   a. Please provide the public health need for this product (1-2 sentences)
      Though the potential burden of the disease is high, the natural course of the illness is very long and only a minority of patients develops serious complications. Recently new drugs (NUC) were registered for this indication and the standard regimen is now a triple therapy of PEG IFN + Ribavirin + NUC (either telaprevir or boceprevir) which offers a modest increase in response and a relatively high burden of side effects to be monitored closely (H12 service needed).
      Active injection-drug users are the source of most cases of HCV transmission in the United States and thus prevention programs should have a prominent role.
      A public health perspective needs considering HCV prevalence by age groups.
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
      The guidelines listed in the application EASL and AASLD are recommending this treatment (though these guidelines are not currently using GRADE methodology to develop their recommendations)

5. **Are there special requirements for use or training needed for safe/effective use?**
   If yes, please provide details in 1-2 sentences

6. **Is the proposed product registered by a stringent regulatory authority?**
   Yes ☑ No

7. **Any other comments**
   The application stressed the comparison between the 2 IFN alfa (2a and 2b) which is probably of secondary importance in this context.
8. What is your recommendation to the committee (please provide the rationale)

Though the response to dual therapy (PEG IFN + ribavirin) is a well established therapeutic option, overall the treatment is an effective one for HCV genotypes 2 and 3 and clearly less effective for genotypes 1 and 4.

It could be considered for inclusion but the WHO Panel should express a judgment on the overall risk/benefit profile and define its present role in therapy also with respect to the fact that the present standard for more severe cases seems to require the addition of a third drug (telaprevir or boceprevir).