17 March 2016
EMA/PRAC/188631/2016

PRAC List of questions

To be addressed by the marketing authorisation holders

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure number: EMEA/H/A-20/1438

Daklinza (daclatasvir)	EMEA/H/A-20/1438/C/3768/0016
Exviera (dasabuvir)	EMEA/H/A-20/1438/C/3837/0017
Harvoni (sofosbuvir/ledipasvir)	EMEA/H/A-20/1438/C/3850/0027
Olysio (simeprevir)	EMEA/H/A-20/1438/C/2777/0019
Sovaldi (sofosbuvir)	EMEA/H/A-20/1438/C/2798/0029
Viekirax (ombitasvir/paritaprevir/ritonavir)	EMEA/H/A-20/1438/C/3839/0018

INN/active substance: daclatasvir, dasabuvir, sofosbuvir/ledipasvir, simeprevir, sofosbuvir, ombitasvir/paritaprevir/ritonavir

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. The MAHs should provide the following information on the use of their product(s):

    a. The current marketing status in the European Union including information related to the approved indication.

    b. The estimated patient exposure in the different EU Member States for the approved indication. This should include use of <product name> in regimens including interferon and in interferon-free regimens, if applicable. This exposure information should provide the following additional information, if available:

        i. Use in HBV/HCV co-infected patients and in patients with evidence of prior HBV infection by country;

        ii. Information on the disease severity, dose and duration of use.

2. The MAHs should consider all available data relating to <product name> use for HBV/HCV co-infected patients and in those with occult HBV infection (HBsAg negative, anti-HBc IgG positive, anti-HBs IgG negative). The use in IFN-free regimens, as well as with interferon, if applicable, should be considered. These analyses should focus on the risk of reactivation of HBV and include comprehensive cumulative reviews of data from clinical trials (including both MAH sponsored and non-sponsored studies), and post-marketing exposure, pharmacoepidemiological studies, including any registries and published literature.

    a. Regarding patients with occult HBV-infection, the MAHs should provide the following data:

        i. Data on the number of patients with anti-HBc IgG antibodies within the phase 2/3 programs and for those who are anti-HBc positive, also data on anti-HBs titers;

        ii. A re-assessment of all cases of severe liver events/unexplained increases of transaminases in clinical trials and confirm whether any of these cases were HBV re-activation;

        iii. A cumulative review of reported hepatic safety events in patients taking <product name> with prior HBV infection from post-marketing spontaneous ADR reports and literature sources. The MAHs should search for all post-marketing reports of hepatic events in cases reporting serological markers indicating prior HBV infection, with particular focus on cases suggestive of HBV reactivation. The MAHs should provide details of all HBV serological markers available in the reports, discuss the clinical outcomes of cases where reactivation occurred and any hepatic events associated with the reactivation;

        iv. Based on the above, please discuss the estimated risk/incidence of hepatitis B reactivation in patients who are anti-HBc positive/HBsAg negative and consider any identifiable risk factors.

b. Regarding the HBV co-infection the MAHs should provide the following:

   i. Any available clinical trial or other data on the treatment of HCV with <product name> in the presence of HBV co-infection. Discuss whether there are any ongoing or planned trials in such patients. HBV-DNA levels during hepatitis C therapy and post treatment should be provided if available and considered for any planned studies as part of the response.
   ii. A cumulative search of all spontaneous reports in subjects with HBV co-infection, searching for cases of hepatic events in reported concurrent HBV infection. Additionally, a review of literature sources should be conducted as well as a discussion on any hepatic events, during or after HCV therapy, linked to hepatitis B co-infection.

3. The MAHs should discuss the possible mechanism of HBV reactivation in patients treated with <product name> on the basis of pre-clinical, clinical, epidemiological and published data. In this context, the MAHs should discuss whether the proposed mechanisms could also favour reactivation of other viral infections.

4. The MAHs should discuss the potential for HBV reactivation on the safe and effective use of their product in HBV/HCV co-infected patients and HCV patients with occult HBV infection and consequently to:

   a. Propose how data on HBV reactivation may be reflected in the product information (SmPC, PL).

   b. Consider measures to further minimise the impact of potential reactivation of HBV, including monitoring of HBV-related parameters during and after treatment for HCV, as well as recommendation for therapy against HBV in such patients.