14 April 2016
EMA/PRAC/196081/2016

Addendum to PRAC List of questions adopted on 17 March 2016

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 perform a comprehensive review of data from clinical trials and observational studies (including both MAH-sponsored and non-sponsored studies) regarding cases of hepatocellular carcinoma (HCC) in chronic hepatitis C patients who achieved sustained virological response (SVR) after treatment with <product name>, analysing over time:

    a) the recurrent cases in patients with history of HCC;

    b) the incident cases in chronic hepatitis C (cirrhotic and non-cirrhotic) patients.

    The MAHs should compare the results with the expected rate over time in cohorts of patients with chronic hepatitis C not treated with interferon-free direct-acting antivirals, justifying such selection.

    Additionally, the MAHs should analyse the risk factors, apart from the progression disease status, that could predispose to the appearance/early recurrence of hepatocellular carcinoma after direct-acting antivirals treatment.

2. The MAHs should perform a systematic review of available publications/congress abstracts:

    a) on the incidence of HCC in patients achieving SVR with direct-acting antivirals;

    b) on the rate/time to recurrence of HCC in patients previously in complete response, who achieve SVR with direct-acting antivirals.

3. The MAHs should discuss any possible biological mechanisms by which anti-HCV therapy with <product name> may favour the induction of new hepatocarcinoma, or earlier recurrence of prior hepatocarcinoma. Additionally, the impact of direct-acting antiviral treatment on immune or inflammatory response and potential clinical consequences should be discussed.

4. On the basis of the responses to the above questions, the MAHs should propose measures to minimise the risk of hepatocarcinoma if appropriate.

5. The MAHs should provide proposals to gather new evidence to characterise the risk of de novo occurrence of hepatocarcinoma in chronic hepatitis C patients and the early recurrence of hepatocarcinoma in patients exposed to <product name>. These should include proposals for clinical/epidemiological studies.