NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission:

Product(s) Name(s) Procedure name	Daklinza (daclatasvir) Exviera (dasabuvir) Harvoni (sofosbuvir/ledipasvir) Olysio (simeprevir) Sovaldi (sofosbuvir) Viekirax (ombitasvir/paritaprevir/ritonavir) Direct-acting antivirals indicated for treatment of hepatitis C (interferon-free)
Active Substance(s)	See above
Pharmaceutical form(s)	All pharmaceutical forms
Strength(s)	All strengths
Route(s) of administration	All routes of administration
Marketing Authorisation Holder(s)	Bristol-Myers Squibb Pharma EEIG AbbVie Ltd Gilead Sciences International Ltd Janssen-Cilag International N.V.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection is not uncommon due to overlapping transmission modes. HCV is known to cause suppression of HBV replication in co-infected patients[i]. The virological and molecular aspects of HBV/HCV coinfection are not fully comprehended. Although liver disease activity and progression are generally more severe in the presence of double infection[ii], an inverse relationship in the replicative levels of the two viruses exists, suggesting direct or indirect viral interference[iii,iv,v]. The European Association for the Study of the Liver (EASL) recommendations on treatment of hepatitis C 2015 make reference to the potential risk of HBV reactivation during or after HCV clearance[vi].

Loss of HBV suppression following interferon-based HCV treatment may lead to increase in HBV replication, however such increase is typically small and severe hepatitis appears to be rare as interferon therapy also has an anti-HBV action (Crockett and Keeffe, 2005).

Over the last few years, the treatment paradigm of chronic hepatitis C has changed considerably, with the development of new direct acting antivirals, providing interferon-free treatment options (Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax). Direct acting antivirals target specific non-structural proteins of the HCV and result in disruption of viral replication and infection. The risk of HBV reactivation may be greater with newer HCV treatment regimens, given their increased potency against HCV and lack of anti-HBV activity.

The number of chronically infected patients with HCV worldwide is estimated to be about 160 million. The exact number of HBV/HCV co- infected patients is unknown. Data from Spain[vii], Italy[viii], Japan, Taiwan, and Iran have shown that approximately 10-15% of patients with chronic HBV infection are also infected with HCV.

Recent literature describes cases of HBV viral load increase after a rapid decline of HCV viral load in patients treated with direct acting antivirals in interferon-free regimens[ix,x,xi,xii,xiii], and further cases have been identified in Eudravigilance. Patients who are co-infected with HBV/HCV are known to be more likely to have severe liver disease, and replicating HBV in co-infected patients is likely to lead to further liver inflammation. Some of the cases identified with direct acting antivirals had serious outcomes, with worsening of hepatic status and at least one case where the patient required liver transplantation. The authors of an article which describes two cases (Collins et al., 2015) hypothesise that HCV treatment with potent, interferon-free, direct acting antiviral in co-infected patients may lead to a suppression of the inhibitory effect of HCV on HBV replication, no longer compensated by the inhibitory effect of interferon.

The seriousness of the events, the need for intervention on HBV reactivation and the biological plausibility of the reactivation warrant further investigation into this issue which is not currently described in the product information of the medicinal products subject to this procedure.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal products Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax. The EC requests the Agency to give its opinion as soon as possible and by 28 February 2017 at the latest on whether a regulatory action with regard to the marketing authorisation for these products is necessary.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Signed 

Date 03/03/2016

Robert Vanhoorde

Head of Medicines: policy, authorisation and monitoring

Health and Food Safety Directorate General

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