ADDENDUM TO NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004 (procedure number EMEA/H/A-20/1438)

This is an addendum to the 10 March 2016 notification by the European Commission of a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) concerning the following medicinal products:

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.

On 10 March 2016, the European Commission requested the Agency to assess the data available concerning the risk of hepatitis B reactivation with direct-acting antivirals providing interferon-free treatment options in the treatment of chronic hepatitis C and their impact on the products' benefit-risk balance and to give its opinion under Article 20 of Regulation (EC) No 726/2004 on whether a regulatory action with regard to the marketing authorisation for these products is necessary.

Since the submission of the above mentioned notification, new concerns have arisen about hepatocellular carcinoma in patients treated with direct-acting antivirals (namely, Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax). Results from a study[1] performed between October 2014 and December 2015 in Hepatology Units of four University Spanish hospitals in patients with chronic hepatitis C and previous history of hepatocellular carcinoma treated with direct-acting antivirals suggested unexpected early hepatocellular carcinoma recurrence.

The seriousness of these events, not currently described in the product information of the medicinal products subject to the ongoing Article 20 procedure, warrants further investigation and consideration of adequate measures to optimise the safe and effective use of these medicinal products.

In view of the above, the European Commission extends the scope of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004 to allow consideration of other data and requests the Agency to assess the risk of hepatocellular carcinoma and its impact on the benefit-risk balance for the centrally authorised medicinal products Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax.

Signed [redacted] Date 14/4/2016
Robert Vanhoorde
Head of Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General

1 Reig, M., Mariño, Z., Perelló, C., Iñarrairaegui, M., Ribeiro, A., Lens, S., Díaz, A., Vilana, R., Darnell, A., Varela, M., Sangro, B., Calleja, J.L., Forns, X., Bruix, J., Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution, Journal of Hepatology (2016)