



EUROPEAN MEDICINES AGENCY
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Direct-acting antivirals for hepatitis C: EMA confirms recommendation to screen for hepatitis B

Further studies needed to assess risk of liver cancer with these medicines

The European Medicines Agency (EMA) has confirmed its recommendation to screen all patients for hepatitis B before starting treatment with direct-acting antivirals for hepatitis C; patients infected with both hepatitis B and C viruses must be monitored and managed according to current clinical guidelines. These measures aim to minimise the risk of hepatitis B re-activation with direct-acting antivirals.

Direct-acting antivirals (marketed in the EU as Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax)¹ are important medicines for treating chronic (long term) hepatitis C, a disease of the liver caused by hepatitis C virus.

The review of direct-acting antivirals was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC). It looked into cases² of returning signs and symptoms of previously inactive hepatitis B infection (re-activation) when patients were treated with direct-acting antivirals for hepatitis C.

The hepatitis B re-activation is thought to be the consequence of the rapid treatment-induced reduction in hepatitis C virus (as co-infection is known to suppress the hepatitis B virus) and the lack of activity of direct-acting antivirals against hepatitis B virus.

The PRAC recommendation to include a warning in the prescribing information about hepatitis B re-activation and how to minimise it has now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP).

In addition to data on hepatitis B re-activation, EMA also reviewed data suggesting that patients treated with direct-acting antivirals who have previously been treated for liver cancer could be at risk of their cancer returning early.

The CHMP agreed that companies should carry out a study to evaluate the risk of liver cancer returning with direct-acting antivirals. In this context, further research is also needed on the risk of new liver cancers in patients with chronic hepatitis C and cirrhosis (liver scarring) that are treated with direct-acting antivirals.

¹ Since the start of this review, two other direct-acting antivirals, Eplclusa (sofosbuvir / velpatasvir) and Zepatier (elbasvir / grazoprevir), have been authorised in the EU.

² Around 30 cases of hepatitis B re-activation have been reported to date among the many thousands of patients treated.



The CHMP's opinion will now be passed to the European Commission for a legally binding decision valid throughout the EU.

Information for patients

- Direct-acting antiviral medicines (including Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax) are effective treatments for long-term hepatitis C that can be used without interferons (medicines known to have troublesome side effects).
- If you also have hepatitis B virus infection, direct-acting antivirals for hepatitis C may cause the hepatitis B infection to become active again. Re-activation of hepatitis B may cause serious liver problems.
- You will be tested for hepatitis B before starting treatment with direct-acting antivirals to check if you might be at risk of hepatitis B reactivation.
- If you have both hepatitis B and C virus infections, your doctor will monitor you closely during and after treatment with direct-acting antivirals. You may also receive treatment for hepatitis B.
- Tell your doctor if you have or have had hepatitis B infection. Speak to your doctor if you have any question or concern regarding your treatment.

Information for healthcare professionals

- Cases of hepatitis B re-activation (with severe consequences) have been reported in patients co-infected with hepatitis B and C viruses treated with direct-acting antivirals. The frequency of such re-activation appears to be low.
- Hepatitis B re-activation is thought to be caused by the rapid treatment-induced reduction in hepatitis C virus (as co-infection is known to suppress the hepatitis B virus) and the lack of anti-hepatitis B activity of direct-acting antivirals.
- All patients should be screened for hepatitis B before starting treatment with direct-acting antivirals for hepatitis C; patients co-infected with hepatitis B and C must then be monitored and managed according to current clinical guidelines.
- Further studies are needed to evaluate the risk of recurring or newly diagnosed hepatocellular carcinoma in patients treated with direct-acting antivirals. Companies marketing these medicines have been asked to perform a prospective study to assess the risk of recurrence of previously treated hepatocellular carcinoma, and a prospective cohort study in patients with cirrhosis to assess the incidence and type of *de novo* hepatocellular carcinoma.
- Therapeutic guidelines recommend that, in patients with advanced fibrosis and cirrhosis, surveillance for hepatocellular carcinoma should continue even after sustained viral response has been achieved.

More about the medicines

The review covered the following direct-acting antivirals for treating chronic hepatitis C: Daklinza (daclatasvir), Exviera (dasabuvir), Harvoni (sofosbuvir / ledipasvir), Olysio (simeprevir), Sovaldi

(sofosbuvir) and Viekirax (ombitasvir / paritaprevir / ritonavir). Since the start of this review, two other direct-acting antivirals, Epclusa (sofosbuvir / velpatasvir) and Zepatier (elbasvir / grazoprevir), have been authorised in the EU.

Direct-acting antivirals work by blocking the action of proteins which are essential for making new hepatitis C viruses.

More information on these medicines can be found on EMA's website: ema.europa.eu/Find/medicine/Human_medicines/European_public_assessment_reports.

More about the procedure

The review of direct-acting antivirals for the treatment of hepatitis C was initiated on 17 March 2016 at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004. On 14 April 2016 the scope of the review was extended to include the risk of liver cancer, in addition to the potential risk of hepatitis B re-activation.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

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