EMA reviews direct-acting antivirals for hepatitis C

Recommendation to screen for hepatitis B confirmed but further studies needed to assess risk of liver cancer

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Information on direct-acting antivirals for hepatitis C

- Direct-acting antivirals are important medicines for treating chronic (long term) hepatitis C, a disease of the liver caused by the hepatitis C virus.
- These medicines work by blocking the action of proteins which are essential for making new hepatitis C viruses (viral replication)
- In the EU direct-acting antivirals are marketed as Daklinza, Exviera, Harvoni, Olysio, Sovaldi and Viekirax[1] and are authorised in Malta via centralised procedure:

Active Ingredients	Product Name	Pharmaceutical Form	Classification	Authorisation Number(s)	MAH/license holder
Daclatasvir	Daklinza	Film-coated tablet	POM	EU/1/14/939/001-004	Bristol-Myers Squibb Pharma EEIG
Dasabuvir	Exviera	Film-coated tablet	POM	EU/1/14/983/001	AbbVie Ltd
Sofosbuvir / Ledipasvir	Harvoni	Film-coated tablet	POM	EU/1/14/958/001-002	Gilead Sciences International Ltd
Simeprevir	Olysio	Capsule, hard	POM	EU/1/14/924/001-002	Janssen-Cilag International N.V.
Sofosbuvir	Sovaldi	Film-coated tablet	POM	EU/1/13/894/001-002	Gilead Sciences International Ltd
Ombitasvir / Paritaprevir / Ritonavir	Viekirax	Film-coated tablet	POM	EU/1/14/982/001	AbbVie Ltd

[1] Since the start of this review (initiated on 17/03/2016), two other direct-acting antivirals, Epclusa (sofosbuvir / velpatasvir) and Zepatier (elbasvir / grazoprevir), have been authorised in the EU.

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EMA confirms recommendation to screen for hepatitis B but further studies are needed to assess risk of liver cancer with direct-acting antivirals for hepatitis C

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.

- The review of direct-acting antivirals was carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004. 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 PRAC looked into cases 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.

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

In Malta

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.

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.

For more information on the review of direct-acting antivirals for hepatitis C refer to the EMA press release. More information on these medicines can be found on EMA's website.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on direct acting antivirals. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form (available from: **http://www.medicinesauthority.gov.mt/adrportal**) and sent by mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or email to **postlicensing.medicinesauthority@gov.mt** or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

We thank you for your interest and look forward to hearing your opinion.

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