

Direct acting antivirals (hepatitis C) risk of reactivation of hepatitis B



Quick Read

Testing for hepatitis B virus is recommended at the beginning of therapy with DAAVs for hepatitis C. Monitoring patients who are co-infected with both viruses is also recommended. A possible risk of hepatocellular carcinoma in patients treated with DAAVs is unclear and further data are expected.

The direct acting antivirals (DAAVs) for hepatitis C which are authorized in the European Union are: Daklinza (daclatasvir), Epclusa (sofosbuvir + velpatasvir), Exviera (dasabuvir), Harvoni (ledipasvir + sofosbuvir), Olysio (simeprevir), Sovaldi (sofosbuvir), Viekirax (ombitasvir + paritaprevir + ritonavir), and Zepatier (elbasvir + grazoprevir).

Co-infection with both hepatitis B and C tends to suppress the B virus. It is thought that reactivation of hepatitis B may be a consequence of rapid reduction in hepatitis C viral load induced by DAAVs, and/or the fact that DAAVs for hepatitis C are not active against the hepatitis B virus.

EMA has concluded an assessment on the risk of hepatocellular carcinoma and reactivation of hepatitis B associated with the use of direct acting antivirals used in the treatment of chronic hepatitis C. **Risk of reactivation of hepatitis B** has been confirmed and testing for this virus is recommended in every patient at the beginning of treatment. Patients with hepatitis B and C co-infection should also be monitored in accordance with current clinical guidelines. Although the frequency of hepatitis B reactivation is seemingly low, the inclusion of this warning in the SmPCs (Summaries of Product Characteristics) and PILs (Patient Information Leaflets) of these medicinal products has been recommended.

As for the **risk of hepatocellular carcinoma** in patients on DAAVs, additional studies were considered necessary to assess the risk of both recurrence and de novo appearance. Marketing authorization holders are expected to conduct a prospective study to assess the recurrence of previously treated hepatocellular carcinoma, as well as a prospective cohort study in patients with cirrhosis to assess the incidence and type of de novo hepatocellular carcinoma.

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INTERACTIONS

- A drug-drug interaction between direct acting antivirals (**DAAVs**) used in the treatment of hepatitis C and vitamin K antagonists (such as **warfarin**) can cause **INR reduction**.

[See Bulletin 4-2016](#)

- **Clopidogrel** can inhibit the hepatic metabolism of **repaglinide**, thus **potentiating** its action.

[See Bulletin 1-2016](#)

- **COBICISTAT**, which is used for pharmacokinetic potentiation as part of antiretroviral combination therapy in adults with HIV 1 infection, may **interact with corticosteroids** resulting in increased risk of adrenal adverse effects.

[See Bulletin 6-2016](#)

- The tetracycline **TIGECYCLINE** may be associated with a **reduction in blood serum levels of fibrinogen**.

[See Bulletin 4-2016](#)

- Seventy percent of cases of **drug-induced QT INTERVAL PROLONGATION** occur in the presence of two or more risk factors. In at-risk patients with no therapeutic alternative a baseline ECG should be undertaken, as well as on follow-up, especially once the drug reaches its steady state. QTc red flags: from 470-500 ms in men or from 480-500 ms in women, OR a prolongation of 60 ms or more [$QTc = QT + 0.154(1-RR)$].

[See Bulletin 6-2016](#)

VIRAL REACTIVATION

- **Hepatitis B** virus reactivation is a well-known complication in patients on immunosuppressant **chemotherapy**. It can also occur with exposure to **Bcr-ABL TYROSINE-KINASE INHIBITORS**.

[See Bulletin 1-2016](#)

- Clinical surveillance, MRI evaluation and testing for John Cunningham (JC) antibodies are central for the follow-up of patients on **Tysabri® (NATALIZUMAB)**, in order to allow for early detection of progressive multifocal leucoencephalopathy (**PML**).

[See Bulletin 1-2016](#)

- **Psychiatric** disorders can occur with administration of topical **OXYBUTYNIN**. This medicine should be used with special caution in elderly patients. It is not recommended for children.

[See Bulletin 1-2016](#)

- **AGOMELATIN**, a melatonergic agent and a 5-HT_{2c} antagonist, similarly to other antidepressants, may rarely be associated with **urinary retention**.

[See Bulletin 3-2016](#)

- Dwelling of a **DUODOPA** pump tube in the bowel may be associated with the occurrence of adverse intestinal reactions including **intussusception**.

[See Bulletin 1-2016](#)

- The haemostatic and tissue “glueing” agent **TachoSil®** used in surgery may be associated with the occurrence of intestinal obstruction from the formation of **adhesions**.

[See Bulletin 2-2016](#)

- A recent metaanalysis published in The Lancet points to increased risk of ovarian cancer associated with the use of **postmenopausal hormone replacement therapy (HRT)**. It is not clear whether there is a causal relation but, if so, women on HRT for five years from about 50 years of age may have one additional case of **ovarian cancer** per one thousand users.

[See Bulletin 1-2016](#)

- Exposure to **MITOTANE** for months may be associated with the appearance of **ovarian cysts** which are frequently bilateral and accompanied by ovarian and gonadotropic hormonal changes.

[See Bulletin 2-2016](#)

- **INHALED CORTICOSTEROIDS** are indicated for COAD, but one should be aware of a possible risk of **pneumonia**, so much so that its manifestations can overlap and be mistaken for those of the background condition.

[See Bulletin 2-2016](#)

- **Calciphylaxis** is a rare syndrome of vascular calcification and skin necrosis, of high mortality and relatively obscure pathophysiology. It can be associated with various conditions including renal insufficiency. Rare cases of calciphylaxis have been observed in patients on **WARFARIN**, even in the absence of kidney impairment.

[See Bulletin 3-2016](#)

- There do not seem to be any significant differences among the various products containing **RECOMBINANT FACTOR VIII** in terms of **antibody** development in patients with severe haemophilia A.

[See Bulletin 3-2016](#)

- Patients with an indication for **metformin** can benefit from this therapy **including when their renal function is only moderately reduced** (GFR = 30-59 ml/min). Renal function should be monitored before treatment is started and then annually.

[See Bulletin 4-2016](#)

- When treatment with **FLUCLOXACILLIN** is started the appearance of fever with a generalized rash may point to the occurrence of **acute generalized exanthematous pustulosis**. This antibiotic should be permanently discontinued.

[See Bulletin 6-2016](#)

- Cases of very rapid onset of **serious liver toxicity** (including fatalities) have been reported in patients with **Cockayne syndrome** after starting therapy with systemic **METRONIDAZOLE**.

[See Bulletin 6-2016](#)

PROBLEMS OF USE

- **Abuse or misuse** of **LOPERAMIDE** in high doses may be associated with serious cardiac reactions such as *torsades de pointes*.

[See Bulletin 6-2016](#)

- The labelling and packaging of **LEVETIRACETAM (Keppra®)** oral solution has been optimized by resorting to colour coding and special design, in order to minimize the risk of **accidental overdose**, especially in children, due to the use of the wrong syringe or to medication error.

[See Bulletin 4-2016](#)


MARKET WITHDRAWAL

- **Locabiosol 125 mcg® (FUSAFUNGINE)**, mouth or nasal spray, has been withdrawn on account of a risk of **serious allergic** reactions with limited evidence of therapeutic benefit.

[See Bulletin 2-2016](#)

Educational Materials published on the Infarmed website



Medicinal product (DCI)	Click on the links (in Portuguese)
Quetiapina Ciclum (quetiapine)	 <p>Informação for physicians Informação importante de segurança para médicos prescritores – 1.ª versão aprovada em dezembro de 2016 For psychiatrists, neurologists, internists and family doctors. Published on 22-12-2016</p>

Communications to Healthcare Professionals published on the Infarmed website



Medicinal product (DCI)	Click on topic for details (in Portuguese)
Ammonaps (sodium phenylbutyrate)	<p>Tablets and granules to be used only in the absence of therapeutic alternatives. Published on 22-12-2016</p>

Compiled by Magda Pedro

What do they mean?

ADR Adverse Drug Reaction

EMA European Medicines Agency

MA Marketing Authorization

PIL Patient Information Leaflet

PRAC Pharmacovigilance Risk Assessment Committee (EMA)

SmPC Summary of Product Characteristics

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