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HPRA DRUG SAFETY NEWSLETTER

77TH EDITION

In this Edition

Direct-Acting Antivirals for Hepatitis C: Advice on interaction potential with warfarin and other vitamin K antagonists leading to a reduced international normalised ratio (INR)

Direct-Acting Antivirals (Daklinza, Exviera, Harvoni, Olysio, Sovaldi, Victrelis, Viekirax, Zepatier and Epclusa)* are used to treat chronic hepatitis C virus (HCV) infection. These medicines reduce the amount of HCV in the body by preventing HCV from multiplying, and in most cases, they cure HCV.

A signal of a potential drug interaction leading to a reduced international normalized ratio (INR) has recently been identified with co-administration of Direct-Acting Antivirals and vitamin K antagonists. The case reports on which the signal was based were reviewed by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC has recommended that the product information of Direct-Acting Antivirals should be updated to include a recommendation for close monitoring of INR in patients treated with vitamin K antagonists, as liver function may change during treatment with Direct-Acting Antivirals. Pharmacokinetic studies with warfarin have been performed for Olysio, Viekirax and Exviera. While no change in the pharmacokinetics of warfarin is expected, close monitoring of INR is recommended with all vitamin K antagonists. This is due to liver function changes during treatment with Direct-Acting Antivirals.

Advice to Healthcare Professionals

- As liver function may change during treatment with Direct-Acting Antivirals, it is recommended that INR is closely monitored in patients concurrently treated with vitamin K antagonists.

Key Message

Liver function changes during treatment with Direct-Acting Antivirals may lead to a reduced INR in patients concurrently treated with warfarin and other vitamin K antagonists.

Healthcare professionals should be alert to this potential interaction and closely monitor INR in these patients.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these products will be updated to reflect these recommendations.

** Daklinza (daclatasvir), Exviera (dasabuvir), Harvoni (sofosbuvir/ledipasvir), Olysio (simeprevir), Sovaldi (sofosbuvir), Victrelis (boceprevir) and Viekirax (ombitasvir/paritaprevir/ritonavir). Further details are available on www.hpra.ie and www.ema.europa.eu*

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Advice on potential interaction between cobicistat-containing products and corticosteroids primarily metabolised by CYP3A: risk of adrenal suppression

Cobicistat is a pharmacokinetic enhancer, or 'booster', used as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults. Cobicistat is a selective mechanism-based inhibitor of the cytochrome P450 enzyme subfamily CYP3A. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as elvitegravir, azatanavir and darunavir, which have short half-lives due to CYP3A-dependent metabolism.

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recently reviewed cases of adrenal suppression and Cushing's syndrome linked with an interaction between cobicistat-containing products and corticosteroids that are metabolised by CYP3A.

In light of this signal, the PRAC has recommended that the product information should be updated to reflect that the plasma concentrations of corticosteroids primarily metabolised by CYP3A (including betamethasone, budesonide, fluticasone, mometasone, prednisone and triamcinalone) may be increased when co-administered with cobicistat-containing products, resulting in reduced serum cortisol concentrations.

Co-administration of CYP3A-metabolised corticosteroids with cobicistat is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism, e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use.

Key Message

Cases of adrenal suppression and Cushing's syndrome have been reported in patients concurrently using CYP3A-metabolised corticosteroids and cobicistat.

CYP3A-metabolised corticosteroids should only be co-administered with cobicistat where the benefit to the patient outweighs the risk.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these products will be updated to reflect these recommendations.

* *Cobicistat is a component of the fixed-dose combination products Evotaz (atazanavir/cobicistat) and Rezolsta (darunavir/cobicistat) and single tablet regimens Stribild (elvitegravir/emtricitabine/tenofovir disoproxil fumarate/cobicistat) and Genvoya (elvitegravir/emtricitabine/tenofoviralafenamide/cobicistat), and is also licensed as a monocomponent product (Tybost) for use in conjunction with the protease inhibitors atazanavir or darunavir. Further details are available on www.hpra.ie and www.ema.europa.eu*

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Pro-Epanutin (fosphenytoin)	Medication errors and off-label use in children under 5 years of age.
Zydelig (idelalisib)	Update advice following conclusion of a safety review.
Humalog (insulin lispro)	Important safety information to minimise medication errors.

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Adverse reaction reporting during 2015

The HPRA continues to place great emphasis on encouraging and promoting the submission of adverse reaction reports associated with the use of medicines from its stakeholders. These reports are important to signal potential safety issues from medicines in use and ultimately to assist the HPRA in monitoring the safety of medicines on the Irish market.

During 2015, a total of 2,810 suspected adverse reaction reports were received by the HPRA from healthcare professionals, members of the public and pharmaceutical companies. The breakdown of reports according to their source is outlined in the table below.

Report Source	**%**
Pharmaceutical company	67*
Patient/Consumer	8
Community Care Doctor	4
Community Pharmacist	4
General Practitioner	4
Hospital Pharmacist	4
Nurse	4
Hospital Doctor/Specialists	3
Clinical Trial reports	1
Other	1

* *Reports submitted by pharmaceutical companies will have first been brought to their attention by healthcare professionals, patients and consumers, prior to onward reporting to the HPRA.*

In keeping with experience in other European countries, reporting rates were highest for newly authorised medicines. Medicines subject to additional monitoring accounted for 25% of the reports submitted during 2015. The requirements for additional monitoring, introduced in the context of the pharmacovigilance legislative revisions in 2012, highlight the importance of reporting all suspected adverse reactions associated with the use of these products which are identifiable by a black inverted triangle included on the accompanying package leaflet (PL) and the summary of product characteristics (SmPC).

Individual case reports are followed up by the HPRA, with feedback information provided to reporters, as appropriate. Relevant, anonymised reports (i.e. serious, suspected cases) notified directly to the HPRA by healthcare professionals or members of the public are forwarded to the appropriate marketing authorisation holders (MAHs) and the European Medicines Agency Eudravigilance database for inclusion in signal detection activities. The HPRA also continues to provide details of reports received to the World Health Organisation (WHO) for inclusion on its international database.

Suspected adverse reactions may be reported to the HPRA in a number of ways:

- By submitting an online adverse reaction report form, accessible from the HPRA homepage (www.hpra.ie);
- By printing and completing a copy of our adverse reaction report form from our website and sending to the HPRA via Freepost, or by downloading and submitting by email to medsafety@hpra.ie
- By completing a 'Yellow Card' report and sending to the HPRA using Freepost;
- By telephone to the HPRA Pharmacovigilance section (01 676 4971).

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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