MARCH 2017

HPRA DRUG SAFETY NEWSLETTER

79TH EDITION

In this Edition

Fluconazole - reminder not to use in pregnancy

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently evaluated a signal arising from a registry study which reported an association between the use of oral fluconazole during pregnancy and the risk of spontaneous abortion and stillbirth. Fluconazole is a triazole antifungal agent licensed in Ireland, for treatment and prevention of specified fungal infections in adults and children, under various brand names and in a number of different presentations (capsules, powder for oral suspension, and solution for infusion). Previous studies regarding safety of fluconazole in pregnancy have linked high dose treatment and long-term treatment to birth defects. The recent registry-based cohort study[1] suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester. A statistically significant increased rate for stillbirth was not found (although the study may have been underpowered). This well conducted observational study had some limitations and there was insufficient evidence to support a dose relationship. The registry study was considered, along with a cumulative review of all available data from clinical trials, post-marketing data and literature publications concerning the risk following exposure to fluconazole during pregnancy. In this regard, PRAC has recommended an update to the product information for all formulations of fluconazole-containing medicinal products with respect to the risk of spontaneous abortion. Product information already advises against fluconazole use in pregnancy.

Advice to Healthcare Professionals

- Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.
- Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Key Message

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester. Previous studies have linked high dose treatment and long-term treatment to birth defects.

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary, while fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Any suspected adverse reactions should be reported to the HPRA through the available options (www.hpra.ie).

Further information on fluconazole-containing products is available from www.hpra.ie

Reference

1. *Mølgaard-Nielsen D et al. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. JAMA. 2016: 315(1); 58-67.*

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

SGLT2 inhibitors and risk of lower limb amputation (mainly toe)

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has concluded its review of the risk of lower limb amputation (mainly affecting the toes) associated with sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin and empagliflozin), which are indicated in adults for the treatment of Type 2 diabetes, as monotherapy or in combination with other diabetes medicines.

In May 2016, healthcare professionals were informed, via a Direct Healthcare Professional Communication (DHPC), of a two-fold higher incidence of lower limb amputation (primarily of the toe) which had been seen in the ongoing long-term CANVAS clinical trial with canagliflozin. An increased risk has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin, however data available to date are limited. As all SGLT2 inhibitors share a similar mechanism of action and, as the mechanism leading to an increased amputation risk, or an underlying cause specific to canagliflozin-containing medicines could not be established, a class effect could not be excluded. Therefore, the PRAC review encompassed all of the authorised products within the SGLT2 inhibitor class.

During the recently concluded PRAC review, interim data from two ongoing long-term clinical trials involving patients with or at high cardiovascular risk (CANVAS and CANVAS-R) were considered, along with all related available data from finalised and other ongoing clinical trials and reports from post-marketing surveillance available from the marketing authorisation holders (MAHs) of all authorised SGLT2 containing medicinal products. On the basis of the currently available data, the PRAC concluded that treatment with canagliflozin may contribute to an increased risk of amputation of the lower limb, mainly affecting the toes, but considered that a possible class effect cannot be currently excluded. While further specific risk factors (apart from general risk factors) for amputation events could not be identified, the PRAC recommended that patients should continue to receive advice on routine preventative foot care and maintaining adequate hydration, as general advice to prevent amputation. The product information of all SGLT2 inhibitors will be updated to include a warning of the risk of lower limb amputation (primarily of the toes), highlighting to healthcare professionals and patients the importance of routine preventative foot care. Lower limb amputation will also be included as an uncommon adverse reaction in the product information for canagliflozin-containing products. The warning for canagliflozin-containing products will also highlight carefully monitoring patients with a higher risk for amputation events and that, in patients developing amputation preceding events such as infection or skin ulceration, consideration may be given to discontinuing treatment.

The PRAC concluded that the benefit-risk balance of SGLT2 inhibitor-containing products remains favourable, subject to these amendments to the product information. The PRAC recommendations were endorsed by the Committee for Medicinal Products for Human Use (CHMP) and will now be passed to the European Commission for a final, legally binding, decision which will be applicable in all Member States.

Advice to Healthcare Professionals

- All patients taking an SGLT2 inhibitor should be counselled on the importance of routine preventative foot care.
- Patients taking canagliflozin, with risk factors for amputation events, such as previous amputation, existing peripheral vascular disease or neuropathy, should be monitored carefully and counselled on the importance of maintaining adequate hydration.
- Patients should be counselled to notify their healthcare professional if they develop ulceration, discolouration, new pain or tenderness in their feet.
- Treatment discontinuation should be considered for patients taking canagliflozin who develop amputation preceding events, for example, lower extremity skin ulcer, infection, osteomyelitis or gangrene.
- Any suspected adverse reactions should be reported to the HPRA through the available options (www.hpra.ie).

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Key Message

An increase in cases of lower limb amputation, primarily affecting the toes, has been observed in patients taking the SGLT2 inhibitor canagliflozin compared with those taking placebo in two ongoing clinical trials. While available data to date is limited, a risk cannot be excluded for the other medicines within the same class, dapagliflozin and empagliflozin.

Patients should be advised on routine preventative foot care and maintaining adequate hydration as a general advice to prevent amputation.

Therapy discontinuation should be considered if patients taking canagliflozin develop significant foot complications such as infection or ulcers.

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

SGLT2 inhibitor-containing products include Forxiga, Xigduo, Jardiance, Synjardy, Edistride, Ebymect, Invokana and Vokanamet. Further details are available on www.hpra.ie and www.ema.europa.eu

Reports of keratoacanthoma with ingenol mebutate

Picato (ingenol mebutate) is indicated for the cutaneous treatment of non-keratotic, non-hypertrophic actinic keratosis in adults, and is available as a gel formulation in two strengths: 150 micrograms/gram (0.015%) for use on the face and scalp over a three day course of treatment and 500 micrograms/gram (0.05%) for application to the trunk and extremities for two consecutive days. The content of one tube covers a treatment area of 25 cm^2. The mechanism of action of ingenol mebutate has not yet been fully characterised, although in vitro and in vivo models have demonstrated a dual mode of action through inducing local lesion cell death and promoting a local inflammatory response.

Reports of keratoacanthoma occurring within the treatment area with a time to onset ranging from weeks to months following use of ingenol mebutate gel have been received from a post-authorisation clinical trial. The trial was conducted with an investigational product of ingenol mebutate 600 micrograms/gram (0.06%) gel on treatment areas of 250 cm^2 and included a large group of severely sun-damaged patients. A higher incidence of keratoacanthoma inside the area treated with ingenol mebutate, compared with vehicle, was observed.

Based on a review of the available evidence generated from clinical trial and post marketing experience, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the risk-benefit balance of medicinal products containing ingenol mebutate remains unchanged but recommended that the product information for Picato should be updated to include information on reports of keratoacanthoma with advice for patients to be vigilant for any new lesions developing within the treatment area. Healthcare professionals should be aware of the following:

Advice to Healthcare Professionals

- Patients should be advised to be vigilant for any lesions (new scaly red patches, open sores, elevated or warty growths) which develop within the treatment area, and to seek medical advice immediately should any occur.
- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for these medicines will be updated shortly with this information.
- Any suspected adverse reactions should be reported to the HPRA through the available options (www.hpra.ie).

Key Message

There have been reports of keratoacanthoma occurring within the area treated with ingenol mebutate, with a time to onset ranging from weeks to months.

Healthcare professionals should advise patients to be vigilant for new lesions developing within the treatment area, and to immediately consult their doctor should any occur.

Further details on Picato are available on www.hpra.ie and www.ema.europa.eu

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

Adverse reaction reporting - reminder

The HPRA greatly appreciates the contribution of busy healthcare professionals in reporting suspected adverse reactions which aids in facilitating the continued surveillance of the safety of medicines. While the time-consuming nature of form-filling and the provision of follow-up is recognised and acknowledged; the collection and evaluation of comprehensive reports is essential to ensure that appropriately detailed case information is available for the continuous surveillance of the safety of medicines. Such reports are essential for the HPRA to ensure that regulatory action/proposals take account of all available data. There are several options in place for reporting suspected adverse reactions to the HPRA. These are as follows:

- By following the links ('Report an Issue' tab) to the online reporting options accessible from the HPRA website homepage (www.hpra.ie);
- Using the downloadable report form also accessible for the HPRA website, which may be completed manually and submitted to the HPRA via 'freepost';
- Using the traditional 'yellow card' report, which also utilises a freepost system. 'Yellow cards' are available from the HPRA Pharmacovigilance department on request.
- By telephone to the HPRA Pharmacovigilance section (01-6764971).

Since July 2012, when new legislation came into force, patients and consumers across the EU were enabled to directly report any suspected adverse reactions they may have experienced to their national reporting system. Information on this option is available from the HPRA website and the package leaflet that accompanies medicines and has also been highlighted via patient organisations. It is HPRA practice to routinely check all reports received for possible duplicates of cases received from other sources and to collate all relevant information related to case reports, as far as possible.

The revised legislation also introduced the concept of additional monitoring, previously highlighted in the DSN (editions 50 and 53), to support prompt identification of any new safety hazards. Healthcare professionals and patients are particularly encouraged and reminded to report all adverse reactions associated with the use of these medicines, identifiable by an inverted black triangle on the product information. An explanatory statement is included both in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL):

▼ This medicinal product is subject to additional monitoring

The European Medicines Agency (EMA) first published the list of medicines subject to additional monitoring in April 2013 (which is accessible from the HPRA and EMA websites), with an increased focus on reporting of suspected adverse reactions associated with the products concerned. This list is reviewed and updated as necessary, following consideration by the Pharmacovigilance Risk Assessment Committee (PRAC) at its monthly meetings. Medicines remain on the additional monitoring list for a five year period, or until PRAC decide to remove it from the list.

Key Message

All products subject to additional monitoring are identifiable by a black inverted triangle accompanied by an explanatory statement in the product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)). Reports of suspected adverse reactions to these medicines are particularly valuable for regulatory monitoring purposes.

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

PRODUCT	SAFETY ISSUE
Flolan (epoprostenol)	New formulation – difference in storage and administration.
Braltus (tiotropium)	Advice to minimise the risk of medication error.
Ammonaps (sodium phenylbutyrate)	Advice to use only when other sodium or glycerol phenylbutyrate-containing medicines cannot be used instead.

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

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority