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In this edition

Fluconazole: Update on pregnancy outcomes following use and new advice for women of childbearing potential

Key Message

- **Product information updates:** recent updates have been made to reflect available data on abnormal pregnancy outcomes as well as new advice on use in women of childbearing potential.
- **Patient advice:** before initiating treatment in women of childbearing potential, inform the patient of the potential risks to the foetus.
- **Washout period:** after single dose treatment, a washout period of one week is recommended before pregnancy.
- **Contraception:** for longer courses of treatment, contraception may be considered, as appropriate, in women of childbearing potential throughout the treatment period and for one week after the final dose.
- **Reminder of existing advice on use in pregnancy:** fluconazole should not be used in standard doses and short-term treatments unless clearly necessary, and in high doses and/or in prolonged regimens except for potentially life-threatening infections.

Fluconazole is a member of the class of triazole antifungal agents and a potent and specific inhibitor of fungal sterol synthesis. Fluconazole containing medicines are indicated in the treatment and prophylaxis of a wide range of fungal infections, including cryptococcosis, systemic candidiasis, mucosal candidiasis, genital candidiasis, prevention of fungal infections in patients with malignancy, and deep endemic mycoses in immunocompetent patients*.

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Following a review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), updates to product information** for fluconazole containing medicines were recommended to reflect available data on abnormal pregnancy outcomes, as follows:

Risk of spontaneous abortion

Observational studies suggest an increased risk of spontaneous abortion in women treated with fluconazole during the first and/or second trimester compared to women who were either not treated with fluconazole or received topical azoles during the same period[1].

Risk of cardiac malformations

Available epidemiological studies on cardiac malformations with the use of fluconazole during pregnancy provide inconsistent results. However, a meta-analysis of five observational studies including several thousand pregnant women exposed to fluconazole during the first trimester found a 1.8 to 2 fold increased risk of cardiac malformations when compared to no fluconazole use and/or topical azoles use[2].

Other birth defects

Case reports describe a pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during pregnancy for three months or more in the treatment of coccidioidomycosis. The birth defects seen in these infants include brachycephaly, ear dysplasia, giant anterior fontanelles, femoral bowing and radio-humeral synostosis. A causal relationship between fluconazole use and these birth defects is uncertain.

Advice for healthcare professionals

Based on the review of available data on adverse pregnancy outcomes, the EMA's PRAC has recommended new advice on use of fluconazole in women of childbearing potential:

- Before starting treatment in women of childbearing potential, healthcare professionals should inform patients of the potential risks to the foetus.
- After a single dose treatment, a washout period of one week is recommended before becoming pregnant.
- For longer courses of treatment, contraception may be considered, as appropriate, in women of childbearing potential throughout the treatment period and for one week after the final dose.
- Healthcare professionals are reminded of existing advice that fluconazole should not be used during pregnancy in standard doses or for short-term treatments unless absolutely necessary. Additionally, high doses or prolonged use of fluconazole should only be considered during pregnancy for treating potentially life-threatening infections.

* *Further details on fluconazole products are available at www.hpra.ie.*

** *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie.*

References:

1. *Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. JAMA. 2016 Jan 5;315(1):58-67.*
2. *Budani MC, Fensore S, Di Marzio M, Tiboni GM. Maternal use of fluconazole and congenital malformations in the progeny: A meta-analysis of the literature. Reprod Toxicol. 2021; 100:42-51.*

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Finasteride and dutasteride: Commencement of EU review regarding association with suicidal ideation and behaviours

Key Message

- **EU review:** the European Medicines Agency (EMA) has initiated a review of medicines containing finasteride and dutasteride following concerns regarding association with suicidal ideation and behaviours. The review will evaluate the impact of suicidal ideation and behaviours on the benefit-risk balance of these medicines.
- **Suicidal ideation:** the review follows a recent update to product information for finasteride to include suicidal ideation as a possible adverse reaction.
- **Reminder of existing advice:** healthcare professionals are reminded of the existing special warning and precautions for finasteride regarding mood alterations such as depressed mood, depression and, less frequently, suicidal ideation.

Finasteride and dutasteride* are members of the class of 5-alpha reductase inhibitors, which work by preventing the enzyme 5-alpha reductase (5-AR) from converting testosterone into 5-alpha-dihydrotestosterone (DHT). DHT is involved in hair loss and the enlargement of the prostate. By inhibiting 5-AR, finasteride and dutasteride decrease levels of DHT, thereby slowing hair loss, stimulating hair growth, and reducing the size of the prostate.

In Ireland, medicines containing finasteride (1 mg tablets) are authorised for the prevention of hair loss and stimulation of hair growth in men aged 18 to 41 years with early-stage androgenic alopecia. Additionally, in Ireland, medicines containing finasteride (5 mg tablets) and dutasteride (0.5 mg capsules) are authorised for the treatment of symptoms of benign prostatic hyperplasia (BPH).

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has initiated a review of all medicines authorised in the EU which contain finasteride or dutasteride in response to concerns about suicidal ideation and behaviours. The review follows a recent update to the product information for finasteride tablets, in which suicidal ideation was added as a possible adverse reaction**.

Whilst the review is ongoing, healthcare professionals are reminded of product information for these medicines. The product information for finasteride-containing medicines authorised in Ireland advises on the monitoring of patients and management if psychiatric symptoms occur during treatment.

The SmPC for dutasteride lists depression as a potential adverse effect.

During the review, PRAC will assess all available data linking finasteride and dutasteride to suicidal ideation and behaviours. Following the outcome of the review, should updated advice be recommended, this will be communicated to healthcare professionals, as appropriate.

* *Further details on products authorised in Ireland containing Finasteride or Dutasteride are available at www.hpra.ie.*

** *To note, not all product information (PI) for all finasteride brands has been updated at the time of publishing.*

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Omega-3-acid ethyl ester medicines: dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or risk factors

Key Message

- **Atrial fibrillation:** systematic reviews and meta-analyses of randomised controlled trials highlighted a dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or risk factors treated with omega-3-acid ethyl esters compared to placebo. The observed risk of atrial fibrillation was found to be highest with a dose of 4 g /day.
- **Advice for patients:** healthcare professionals should advise patients to seek medical attention if they develop symptoms of atrial fibrillation.
- **Treatment discontinuation:** if atrial fibrillation develops, treatment with these medicines should be permanently discontinued.

Medicinal products containing omega-3 ethyl esters* are indicated for reducing triglyceride levels when the response to diet and other non-pharmacological measures has proved inadequate.

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) assessed data from several systematic reviews and meta-analyses of large randomised controlled trials (RCTs) that enrolled over 80,000 patients, mostly with cardiovascular diseases or risk factors. These studies investigated omega-3 fatty acid treatment on cardiovascular outcomes compared with placebo. Data from these studies showed that patients with established cardiovascular diseases or risk factors who were treated with omega-3-acid ethyl esters had a dose-dependent increased risk of atrial fibrillation (AF) compared to those given a placebo. This observed risk was highest with a daily dose of 4 grams.

The most relevant evidence came from three meta-analyses, including one by Lombardi et al.[1], which highlighted an increased risk of incident AF with omega-3 fatty acid supplementation compared to placebo [IRR 1.37, 95% CI (1.22–1.54), P<0.001]. Another meta-analysis by Gencer et al.[2], found a higher risk of AF with doses >1g/day (HR 1.49, 95% CI 1.04–2.15, P=0.042) compared to ≤1g/day (HR 1.12, 95% CI 1.03–1.22, P=0.024). And a third meta-analysis by Yan et al.[3], also highlighted that omega-3 fatty acid supplementation is associated with an increased risk of AF (RR 1.32 95% CI 1.11-1.58; P=0.002).

As a result of this review, the PRAC has recommended updates to the product information to reflect available data.

Healthcare professionals should advise patients to seek medical attention if they develop symptoms of atrial fibrillation, such as light-headedness, asthenia, palpitations or shortness of breath. If atrial fibrillation develops, treatment with these medicines should be permanently discontinued.

A Direct Healthcare Professional Communication (DHPC) has been distributed by the marketing authorisation holder in Ireland in relation to these updates.

** Further details on products containing Omega-3 ethyl esters are available at www.hpra.ie.*

References:

1. *Lombardi M, Carbone S, Del Buono MG, Chiabrando JG, Vescovo GM, Camilli M, Montone RA, Vergallo R, Abbate A, Biondi-Zoccai G, Dixon DL, Crea F. Omega-3 fatty acids supplementation and risk of atrial fibrillation: an updated meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother. 2021 Jul 23;7(4):e69-e70. doi: 10.1093/ehjcvp/pvab008. PMID: 33910233; PMCID: PMC8302253.*
2. *Gencer B, Djousse L, Al-Ramady OT, Cook NR, Manson JE, Albert CM. Effect of Long-Term Marine ω-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. Circulation. 2021 Dec 21;144(25):1981-1990. doi: 10.1161/CIRCULATIONAHA.121.055654. Epub 2021 Oct 6. PMID: 34612056; PMCID: PMC9109217.*
3. *J Yan, M Liu, D Yang, Y Zhang, F An, The most important safety risk of fish oil from the latest meta-analysis?, European Journal of Preventive Cardiology, Volume 29, Issue Supplement_1, May 2022, zwac056.186, https://doi.org/10.1093/eurjpc/zwac056.186*

Product information updates recommended by the Pharmacovigilance Risk Assessment Committee

The HPRA is highlighting a selection of recommendations made by the PRAC to update product information for medicines in clinical use. The PRAC, in which the HPRA participate, are responsible for assessing and monitoring the safety of medicines. Healthcare professionals (HCPs) are reminded to regularly check the HPRA or EMA websites for current product information concerning medicines.

Pramipexole: Augmentation of Restless Leg Syndrome

Pramipexole is indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome. Pramipexole is also indicated in adults for the treatment of the signs and symptoms of idiopathic Parkinson's disease alone or in combination with levodopa.

- Treatment of Restless Leg Syndrome with pramipexole can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities.
- Before starting treatment for Restless Leg Syndrome, patients should be made aware that augmentation may occur. They should be advised to consult their HCP if they encounter any symptoms suggestive of augmentation.
- The lowest effective dose should be used as the risk of augmentation may increase with higher dose.
- In cases where augmentation is suspected, adjusting the dose of pramipexole to the lowest effective dose or discontinuation should be considered.

Rotigotine (Neupro transdermal patch): Dystonic reactions in Parkinson's disease

Rotigotine is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy or in combination with levodopa. Rotigotine is also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.

- Product information for rotigotine has been updated to include a warning that dystonic reactions have been occasionally reported in patients with Parkison's disease following initiation or incremental dose increase of rotigotine.
- These types of reactions reported include dystonia, abnormal posture, torticollis and pleurothotonus (also known as Pisa Syndrome).
- Although dystonic reactions may be a symptom of Parkinson's disease, the symptoms in some of these patients have improved after the reduction or withdrawal of rotigotine.
- If a dystonic reaction occurs, the dopaminergic medication regimen should be reviewed and a dose adjustment of rotigotine considered.

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Paxlovid▼ (nirmatrelvir; ritonavir): Life-threatening and fatal drug-drug interactions with certain immunosuppressants

Paxlovid is indicated for treating COVID-19 in adults who do not require supplemental oxygen and are at increased risk for progressing to severe COVID-19.

- Paxlovid is a potent CYP3A inhibitor and can increase plasma concentrations of other medicines that are metabolised by CYP3A when taken together, potentially causing serious, sometimes fatal, drug interactions.
- Interactions with immunosuppressants like calcineurin inhibitors (ciclosporin, tacrolimus) and mTOR inhibitors (everolimus, sirolimus) have been reported. Co-administration should only occur with close, regular monitoring of immunosuppressant serum levels, both during and after Paxlovid treatment.
- Paxlovid is contraindicated for patients on medicines with highly dependent on CYP3A for clearance, such as voclosporin, due to the risk of serious or life-threatening reactions. Managing these interactions requires a multidisciplinary approach, weighing the benefits of Paxlovid against the risks of drug interactions.
- For detailed information on drug interactions, refer to the Direct Healthcare Professional Communication (DHPC) issued in March 2024 and the current product information*.

* *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.ema.europa.eu.*

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

PRODUCT	SAFETY ISSUE
Hydroxycarbamide-containing medicinal products	Potential interference with continuous glucose monitoring systems
Oral Retinoids (acitretin and isotretinoin)	Reminder of the Pregnancy Prevention Programme
Medroxyprogesterone acetate	Risk of meningioma and measures to minimise this risk
5-fluorouracil (i.v.)	In patients with moderate or severe renal impairment, phenotyping for dihydropyrimidine dehydrogenase (DPD) deficiency by measuring blood uracil levels should be interpreted with caution

Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at http://www.hpra.ie/report, which include an online report form.

All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted to the EMA's EudraVigilance database, where they are available for analysis and to support early detection and monitoring of possible safety signals.

Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

A privacy notice relating the to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available at www.hpra.ie