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HPRA DRUG SAFETY
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119TH EDITION

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Finasteride and dutasteride: Outcome of EU review regarding risk of suicidal ideation

Key Messages

- **Suicidal ideation:** following an EU review of available data, suicidal ideation is considered an adverse reaction of oral finasteride containing medicines, mainly reported in patients treated for androgenic alopecia (AGA), and new advice to manage this risk has been recommended.
- **New recommendations for patients treated for androgenetic alopecia (AGA):**
  - Advise patients treated with oral finasteride for AGA to stop treatment and seek medical advice if they experience depressed mood, depression or suicidal ideation.
  - Sexual dysfunction that may contribute to mood alterations, including suicidal ideation has been reported in some patients treated for AGA. Inform patients to seek medical advice if they experience sexual dysfunction and consider discontinuation of treatment.
  - To further highlight this risk for patients treated for AGA, a patient card will be available in the package of finasteride 1 mg to highlight the risks of depressed mood, depression, suicidal ideation and sexual dysfunction reported with finasteride.
- **Dutasteride authorised for benign prostatic hyperplasia (BPH) indications:**
  - Despite the insufficient evidence to establish a direct association of suicidal ideation with dutasteride, and based on the common mechanism of action for medicinal products of the class of 5-alpha reductase inhibitors, patients treated with dutasteride should be recommended to seek prompt medical advice if symptoms of mood alterations occur.

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Background

Finasteride and dutasteride* are 5-alpha reductase inhibitors that reduce dihydrotestosterone (DHT) levels by inhibiting the enzyme 5-alpha reductase. Finasteride is an inhibitor of the enzyme 5-alpha-reductase types 1 and 2 with a greater affinity for type 2. Dutasteride targets both isoforms of this enzyme. DHT is involved in the pathophysiology of androgenic alopecia (AGA) and benign prostatic hyperplasia (BPH).

In Ireland, finasteride 1 mg tablets are authorised for the treatment of early-stage AGA in men aged 18 to 41 years[1]. Additionally, finasteride 5 mg tablets and medicines containing dutasteride 0.5 mg are authorised for the treatment of symptoms of BPH.

For finasteride- and dutasteride-containing medicinal products, some psychiatric disorders are known risks and are already reflected in the product information. An EU review commenced to examine concerns regarding a risk of suicidal ideation, as outlined in Edition 117 of the HPRA Drug Safety Newsletter. The scientific review, undertaken by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), has concluded, and the PRAC have issued new recommendations and advice, which are outlined below.

Further regulatory steps will be completed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human medicines (CMDh) and the European Commission, for a legally binding decision to complete the regulatory process.

PRAC recommendations

As part of the scientific review, the EMA's PRAC reviewed the available data, including data from clinical trials, case reports, the scientific literature and information received during the review from the public. The existing warnings and advice available for these products concerning mood disorders were considered.

The PRAC assessed 325 relevant case reports of suicidal ideation identified in EudraVigilance, the EU database of suspected adverse reaction reports. This included 313 cases were reported for finasteride and 13 for dutasteride (1 case reported for both). Most cases involved patients treated for AGA, while a 10 times lower number of cases were reported for patients treated for BPH. These numbers should be considered in the context of an estimated exposure of approximately 270 million patient years for finasteride and 82 million patient years for dutasteride.

Overall, the PRAC concluded that regarding suicidal ideation and behaviours reported with 5-alpha reductase inhibitors, the level of evidence for these events differs according to the respective indications, active substances and formulations, and has made recommendations accordingly, as set out below.

Finasteride 1 mg (androgenetic alopecia)

- Suicidal ideation is an adverse reaction of oral finasteride products with a frequency not known, meaning that it cannot be estimated from the available data.
- The product information already includes warnings on mood alterations, including suicidal ideation, together with a recommendation to stop treatment and seek prompt medical advice if these symptoms occur.
- In addition, the review identified cases of suicidal ideation in which sexual dysfunction contributed to the development of mood alterations, including suicidal ideation.
- Sexual dysfunction is a known adverse reaction of finasteride, with persistence of sexual dysfunction (including decreased libido, erectile dysfunction and ejaculation disorders) reported in post-marketing use, including after discontinuation of treatment.
- Warnings and precautions for use will be updated to advise patients to consult their doctor if they experience sexual dysfunction, and discontinuation of the treatment should be considered.
- A new patient card will be included in the package for finasteride 1 mg to inform about the risks of mood alterations, including suicidal ideation, and sexual dysfunction, as well as to advise on the appropriate actions to be taken.

1. *The review included topical finasteride products for the treatment of AGA, however there are no authorised topical finasteride products in Ireland. Where these products are authorised, the product information already contains information about the risks of mood alterations associated with the use of oral finasteride. There is currently insufficient evidence to support a causal association between topical finasteride and the risk of suicidal ideation. Therefore, no product information update is introduced.*

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Finasteride 5 mg (BPH), including combination products

- The review also confirmed that suicidal ideation is an adverse reaction with the frequency not known (cannot be estimated from the available data).
- The current product information of these formulations already contains a warning on mood alterations, including suicidal ideation, together with the recommendation to seek prompt medical advice if these symptoms occur.
- The review included combination products of finasteride with tadalafil or tamsulosin, but there are no authorised combination products with these active ingredients in Ireland.

Dutasteride 0.5 mg (BPH), including combinations with tamsulosin

- There is insufficient evidence to establish a risk of suicidal ideation with dutasteride.
- However, as a precautionary measure, and based on the evidence for another oral 5-alpha reductase inhibitors, warnings and precautions for use will be updated to inform about the potential risk of suicidal ideation, with a recommendation that patients should seek prompt medical advice if symptoms of mood alterations occur.

Following completion of the regulatory steps, it is planned to implement the above recommendations for authorised medicines in Ireland.

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

Bilastine oral formulations: New warning on the risk of QT prolongation/Torsade de points

Key Messages

- **QT prolongation:** product information for oral formulations of bilastine will include a warning and risk factors for QT prolongation and Torsade de pointes.
- The warning will advise caution when using oral bilastine in patients who are at increased risk of experiencing QT/QTc-prolongation.

Oral bilastine is indicated for the symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria*.

Following a routine review of available post-marketing safety data from clinical trials and from spontaneous cases, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) considered that electrocardiogram QT prolongation is not sufficiently recognised as being a risk associated with oral bilastine use. The PRAC, therefore, recommended that a warning on QT prolongation/Torsades de pointes and the associated risk factors should be reflected in the product information for bilastine oral formulations.

Healthcare professional advice

- Caution should be exercised when administering bilastine to patients who are at increased risk of experiencing QT/QTc-prolongation.
- This includes patients with a history of cardiac arrhythmias; patients with hypokalemia, hypomagnesaemia, hypocalcemia; patients with known prolongation of the QT interval or significant bradycardia; and patients with concomitant use of other medicinal products associated with QT/QTc-prolongation.
- Electrocardiogram QT prolongation has also been reported post-marketing.

** Further details on products authorised in Ireland containing bilastine is available at www.hpra.ie*

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Azathioprine: Update to warning on hepatoxicity and monitoring

Key Messages

- The warning on hepatoxicity associated with azathioprine was updated to reflect that cases of non-cirrhotic portal hypertension/portosinusoidal vascular disease have been reported.
- Early clinical signs include abnormal liver enzymes, mild jaundice, thrombocytopenia, and splenomegaly.
- Patients should be informed about the symptoms of liver injury and are advised to contact their doctor immediately if these occur.

Azathioprine is indicated as an immunosuppressant in solid organ transplantation and in a range of inflammatory conditions (see product information for further details on authorised indications).

Azathioprine is hepatotoxic, and liver function tests should be routinely monitored during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy.

Following a review of the available evidence, the EMA's PRAC has recommended an update to existing warnings to monitor for hepatotoxicity and to reflect that cases of non-cirrhotic portal hypertension/portosinusoidal vascular disease have been reported.

The term non-cirrhotic portal hypertension refers to a heterogeneous group of liver disorders in which the initial abnormality comes from the hepatic vascular system. Portosinusoidal vascular disease is a term that refers to several conditions characterised by an alteration of the small branches of the portal vein. It also includes patients with specific histological alterations but without clinical signs of portal hypertension.

Healthcare professional advice

- Cases of non-cirrhotic portal hypertension/portosinusoidal vascular disease have been reported following use of azathioprine.
- Early clinical signs include liver enzyme abnormalities, mild jaundice, thrombocytopenia, and splenomegaly.
- Additionally, the PRAC advised removing statements that indicate hepatic damage is described primarily in transplant patients.
- Patients should be advised about the symptoms of liver injury and advised to contact their doctor immediately if these occur.

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Mesalazine: New warning regarding the risk of idiopathic intracranial hypertension

Key Messages

- Product information will be updated to include idiopathic intracranial hypertension (pseudotumor cerebri) as a potential risk.
- Patients should be advised to report symptoms of idiopathic intracranial hypertension, such as recurrent or severe headache, visual disturbances, or tinnitus.
- If idiopathic intracranial hypertension occurs, discontinuation should be considered.

Mesalazine (5-aminosalicylic acid) is an intestinal anti-inflammatory agent used in the treatment of different phases of ulcerative colitis and Crohn's disease.

Following a routine review of post-marketing safety data, the EMA's PRAC has recommended adding a warning regarding idiopathic intracranial hypertension to mesalazine medicinal products.

The recommendations are based on a review of available data on benign intracranial hypertension from the literature and spontaneous reports, including, in some cases, a close temporal relationship, a positive de-challenge and/or re-challenge.

Healthcare professional advice

- In accordance with this recommendation, product information will be updated to reflect that idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving mesalazine.
- Patients should be warned of signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, visual disturbances or tinnitus.
- If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.
- Additionally, the product information has been updated to reflect that idiopathic intracranial hypertension is included as an adverse reaction with a frequency not known, meaning it cannot be estimated from available data.

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 to the processing of personal data collected by the HPRA concerning adverse reaction reports is available at www.hpra.ie

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