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HPRA DRUG SAFETY NEWSLETTER

123RD EDITION

In this edition

Methylphenidate: New warning regarding increased intraocular pressure and glaucoma

Key Messages

- **New ocular warnings:** Healthcare professionals should be aware of new warnings regarding increased intraocular pressure and glaucoma associated with methylphenidate-containing medicines, and should advise patients to seek medical attention if they experience symptoms.

Methylphenidate-containing medicines are authorised in Ireland for the treatment of attention deficit hyperactivity disorder*.

Following a routine review of methylphenidate-containing medicines, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended updates to product information, including a new warning on increased intraocular pressure (IOP) and glaucoma (including open-angle and angle-closure glaucoma).

Patients should be advised to contact their doctor in case of experiencing symptoms suggestive of increased IOP and glaucoma. An ophthalmologist should be consulted, and discontinuation of methylphenidate should be considered if IOP increases. Ophthalmologic monitoring of patients with a history of increased IOP is recommended.

In addition, dry eye has been identified as a new possible adverse reaction. Obsessive-compulsive disorder (including trichotillomania and dermatillomania), which is already reflected as a possible adverse reaction for some products, will also now be reflected in product information across all methylphenidate-containing medicines.

** Further details on products containing methylphenidate are available from www.hpra.ie.*

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Topical minoxidil: New warning of hypertrichosis associated with inadvertent exposure in children

Key Messages

- **New warning:** Cases of hypertrichosis (excessive hair growth) in infants have been reported following inadvertent skin contact with areas where caregivers had applied topical minoxidil.
- Patients should be advised to **avoid contact between treated areas and children**.

In Ireland, topical minoxidil-containing products are authorised for the treatment of androgenetic alopecia (pattern hair loss)*. These products are available without prescription in various strengths and formulations, including cutaneous solutions and foams.

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a routine periodic safety review of minoxidil-containing topical products. The review considered published literature and spontaneous reports describing cases of hypertrichosis in infants, which occurred following skin contact with minoxidil application sites of patients (caregivers) using topical minoxidil.

Hypertrichosis in these cases was reversible, within months, once infants were no longer exposed to minoxidil. The PRAC recommended updating the product information to include a warning of hypertrichosis in children following inadvertent topical exposure, and that contact between children and minoxidil application sites should be avoided.

In addition, the outer and immediate packaging of topical minoxidil-containing products will be updated to include a *'Do not ingest'* precaution following review of available data on the accidental ingestion of topical minoxidil products.

** Further details on products containing minoxidil are available from www.hpra.ie*

Mysimba (naltrexone hydrochloride/bupropion hydrochloride): Updated advice to minimise risks of interaction between Mysimba and opioids

Key Messages

- **Risk of reduced opioid effect and interaction:** Mysimba may reduce the effectiveness of opioid analgesics and has been associated with inadequate pain control peri-operatively; rare cases of seizures and serotonin syndrome have also been reported with concomitant serotonergic medicines and opioids.
- **New restrictions on opioid use:** Mysimba must not be used in patients taking opioids or undergoing opioid withdrawal, and patients should avoid opioids during treatment; if opioids are required (e.g. surgery), Mysimba should be stopped at least three days in advance.

Mysimba* is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adults living with obesity, or who are overweight and have at least one weight-related co-morbidity (e.g. type 2 diabetes, dyslipidaemia, or controlled hypertension).

Following a review of available information, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended updates to the product information to minimise the risks of interaction with opioids.

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The updates to the product information take into account reports of insufficient intra- and post-operative analgesia in patients treated with Mysimba. In addition, there have been rare reports of seizures and serotonin syndrome after concomitant use of Mysimba with a serotonergic agent such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) and opioids.

Accordingly, product information was revised to reflect that:

- Mysimba must not be used in patients dependent on opioids, including opioid-containing medicines, patients treated with opioid agonists used in opioid dependence (e.g. methadone, buprenorphine) or patients in acute opioid withdrawal. If opioid use is suspected, a test may be performed to ensure clearance of opioid medication before starting treatment with Mysimba.
- Patients must be warned against the concomitant use of opioids during treatment with Mysimba. If opioid use is required (e.g. due to a planned surgery), Mysimba should be stopped for a minimum of three days before starting opioid treatment.
- In case of emergency surgery in patients potentially treated with Mysimba, there is a risk that the effects of opioids may be reduced.

In addition to the existing physician prescribing checklist, the PRAC recommended that a patient card should be implemented to highlight to patients the need to inform their doctor on the use of Mysimba in case of planned surgery, and to serve as a safety measure in the event of emergency care.

** Further details on Mysimba, including access to the prescriber checklist and patient card, are available from www.hpra.ie*

The HPRA is also highlighting that a Direct Healthcare Professional Communication (DHPC) was recommended by the EMA's Committee for Medicinal Products for Human Use (CHMP) regarding an undetermined long-term cardiovascular risk and new recommendations on annual assessment.

Product information updates recommended by the Pharmacovigilance Risk Assessment Committee

The HPRA highlights a selection of recommendations made by the PRAC to update product information for medicines in clinical use. The approved product information comprises the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie. The PRAC, in which the HPRA participate, is responsible for assessing and monitoring the safety of medicines. Healthcare professionals are reminded to check the HPRA or EMA websites regularly for current product information concerning medicines.

Testosterone (except topical use): pulmonary oil microembolism and haematocrit monitoring

Testosterone (except topical use) is indicated for replacement therapy for male hypogonadism, when testosterone deficiency has been confirmed by clinical features and biochemical tests.

- Testosterone-containing medicines (except for topical use), as with all oily solutions, must be injected strictly intramuscularly and very slowly.
- Pulmonary microembolism of oily solutions can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection, and are reversible.
- Observe patients during and immediately after each injection to allow for early recognition of possible signs and symptoms of pulmonary oily microembolism. Treatment is usually supportive, e.g. by administration of supplemental oxygen.
- Additionally, in patients receiving testosterone replacement therapy concomitantly with SGLT2 inhibitors, monitoring of haemoglobin and haematocrit levels is recommended, as both treatments are associated with an increased risk of erythrocytosis.

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Meropenem: updated warning of drug-induced liver injury and hypokalaemia

Meropenem is indicated in adults and children (3 months and older) for the treatment of certain infections caused by single or multiple susceptible bacteria, and as empiric therapy prior to the identification of the causative organisms. For full details, see the product information for meropenem-containing medicines medicines on www.hpra.ie.

- Product information updates have been recommended for meropenem-containing medicines to reflect risks of drug-induced liver injury (DILI; including hepatitis and liver failure) and hypokalaemia.
- Hepatic function should be closely monitored during treatment with meropenem due to the risk of DILI.
- If severe DILI occurs, treatment discontinuation should be considered as clinically appropriate, and reintroduced only if assessed as essential for treatment.
- Additionally, hypokalaemia was recommended to be included as a potential adverse reaction.

Denosumab: monitoring of bone mineral density following discontinuation

Denosumab is indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer.

- Following denosumab discontinuation, a decrease in bone mineral density (BMD) is expected, leading to an increased risk for fractures. Thus, monitoring of BMD is recommended, and alternative treatment should be considered according to clinical guidelines.

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

PRODUCT	SAFETY ISSUE
Ontozry (cenobamate)	New requirements for liver monitoring due to reports of severe liver injury
Keppra (levetiracetam) Oral Solution (150 ml Bottle for Children Aged 6 Months To 4 Years)	Risk of medication error due to change of dosing syringe

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 in relation to adverse reaction reports is available at www.hpra.ie