March 2025

HPRA DRUG SAFETY NEWSLETTER

118TH EDITION

In this edition

Glatiramer acetate: Anaphylactic reactions may occur months up to years after treatment initiation

Key Message

- **Anaphylactic reactions:** may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment. Cases with a fatal outcome have been reported.
- **Healthcare professional advice:** patients and/or caregivers should be informed about the symptoms and signs of anaphylactic reactions and to seek immediate emergency medical care in the event of an anaphylactic reaction.
- **Treatment discontinuation:** glatiramer acetate must be discontinued if an anaphylactic reaction occurs.

Glatiramer acetate is indicated for treating relapsing forms of multiple sclerosis. It is available as subcutaneous injections in a 20 mg/ml solution (once daily injection) and a 40 mg/ml solution (three-times-weekly injection).*

Anaphylactic reactions

Glatiramer acetate may cause anaphylactic reactions. Based on post-marketing experience, it is estimated that anaphylactic reactions are uncommon (≥1/1,000 to <1/100).

Following a review by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), product information has been updated to reflect that anaphylactic reactions may occur shortly following administration of glatiramer acetate, even months up to years after initiation of treatment. Cases with a fatal outcome have been reported.

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

Healthcare professional advice

- Patients and caregivers should be informed about the signs and symptoms of anaphylactic reactions and instructed to seek immediate emergency medical care if an anaphylactic reaction occurs.
- This is particularly important given the potential for self-administration in a home setting and the seriousness of anaphylactic reactions.
- It is also important to note that some signs and symptoms of an anaphylactic reaction may overlap with post-injection reactions (flushing, chest pain, dyspnoea, palpitations or tachycardia), leading to a potential delay in the identification of an anaphylactic reaction.
- If an anaphylactic reaction occurs, treatment with glatiramer acetate must be discontinued.

The product information for glatiramer acetate-containing medicines has been updated to reflect the new advice. A Direct Healthcare Professional Communication (DHPC) has been issued to inform healthcare professionals of these updates.

* *Currently authorised medicines containing glatiramer acetate include Copaxone and Brabio. Further details, including the approved product information, are available from www.hpra.ie.*

Medroxyprogesterone acetate: Risk of meningioma and measures to minimise the risk

Key Message

- **Increased risk of meningioma:** treatment with high doses of medroxyprogesterone acetate (all injectables and ≥100 mg tablets) is associated with an increased risk of developing meningioma, primarily after prolonged use (several years).
- **For contraception and non-oncological indications:** medicines containing high doses of medroxyprogesterone are contraindicated in patients with meningioma or a history of meningioma. If meningioma is diagnosed in a patient treated with high doses of medroxyprogesterone acetate, treatment must be stopped.
- **For oncological indications:** if a meningioma is diagnosed in a patient treated with high doses of medroxyprogesterone acetate, the need to continue the treatment should be carefully reconsidered on a case-by-case basis, taking into account individual benefits and risks.
- **Monitoring requirements:** patients treated with high doses of medroxyprogesterone should be monitored for symptoms of meningioma in accordance with clinical practice.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has issued new recommendations in relation to the risk of meningioma associated with high doses of medroxyprogesterone acetate (all injectables and ≥100 mg tablets).

In Ireland, the licensed medicine Depo-Provera 150 mg/ml Suspension for Injection* is only indicated for contraception. Medroxyprogesterone acetate is licensed in other EU/EEA countries for oncological indications.

Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
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Increased risk of meningioma with high doses

Meningioma is a rare, most frequently benign tumour that forms from the meninges. Clinical signs and symptoms of meningioma may be non-specific and include changes in vision, hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, or weakness in the extremities. While meningiomas are usually benign, their location may lead to serious consequences and may require surgery.

Based on results from a French epidemiological case-control study[1] an association between medroxyprogesterone acetate and meningioma has been observed. This study was based on data from the French National health data system (SNDS – Système National des Données de Santé) and included a population of 18,061 women who had intracranial surgery for meningioma. Each case was matched to five controls per year of birth and area of residence (90,305 controls). The exposure to medroxyprogesterone acetate 150 mg/3 ml injectable was compared between women who had intracranial surgery for meningioma and women without meningioma. Analyses showed an excess risk of meningioma with the use of medroxyprogesterone acetate 150 mg/3 ml (9/18,061 cases (0.05%) vs. 11/90,305 controls (0.01%), odds ratio (OR) 5.55 (95% CI 2.27 to 13.56)). This excess risk seems to be driven by prolonged use (≥3 years) of medroxyprogesterone acetate 150 mg/3 ml. Although the relative risk of meningioma is significantly increased with the use of high dose medroxyprogesterone acetate, the absolute risks are very small.

No new safety concern regarding a risk of meningioma associated with the use of low-dose (<100 mg) medroxyprogesterone or combination products containing medroxyprogesterone has been identified at this time. Therefore, the recommendations do not apply to lower doses of oral formulations of medroxyprogesterone acetate.

Healthcare professional advice

For contraception and non-oncological indications:

- Medicines containing high-dose medroxyprogesterone acetate must not be used in patients who have a meningioma or have had one in the past.
- If a meningioma is diagnosed in a patient treated with high doses of medroxyprogesterone acetate, treatment must be stopped.

For oncological indications:

- If a meningioma is diagnosed in a patient treated with high doses of medroxyprogesterone acetate, the need to continue the treatment should be carefully reconsidered on a case-by-case basis, taking into account individual benefits and risks.

Patients treated with high doses of medroxyprogesterone acetate should be monitored for signs and symptoms of meningioma in accordance with clinical practice.

A Direct Healthcare Professional Communication (DHPC) was issued in October 2024 concerning this update. Following the recommendations of the EMA's PRAC, product information has been updated as relevant for licensed medicines in Ireland.

References:

1 Roland N, Neumann A, Hoisnard L, Duranteau L, Froelich S, Zureik M et al. Use of progestogens and the risk of intracranial meningioma: national case-control study BMJ 2024; 384 :e078078 doi:10.1136/bmj-2023-078078

** For further details on the medicine, approved product information is available from www.hpra.ie.*

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Product information updates recommended by the Pharmacovigilance Risk Assessment Committee

The HPRA highlights a selection of recommendations made by the Pharmacovigilance Risk Assessment Committee (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 (HCPs) are reminded to regularly check the HPRA or EMA websites for current product information concerning medicines.

Allopurinol: Concomitant use with 6-mercaptopurine or azathioprine should be avoided, as there have been reports of fatal cases.

Allopurinol is indicated for reducing uric acid formation in conditions where deposition has occurred (e.g. gout) or is a predictable clinical risk (e.g. cancer treatment), and certain enzyme-related disorders leading to overproduction of uric acid. See product information for a full list of approved indications.

- Concomitant use of allopurinol with 6-mercaptopurine or azathioprine should be avoided as there have been reports of fatal cases.
- Allopurinol inhibits xanthine oxidase, which can result in increased serum concentrations of azathioprine or 6-mercaptopurine which may reach toxic levels. This may result in consequent life-threatening pancytopenia and myelosuppression if these products are given concurrently.
- If it is determined that co-administration is clinically needed, the dose of azathioprine or 6-mercaptopurine should be reduced to one quarter (25%) of the usual dose of 6-mercaptopurine or azathioprine, with frequent haematologic monitoring ensured.
- Patients should be advised to report signs or symptoms of bone marrow suppression (unexplained bruising or bleeding, sore throat, fever).

Nebivolol: Risk of severe hypoglycaemia when used concomitantly with sulfonylureas.

Nebivolol is a beta-blocker indicated for the treatment of essential hypertension. Some nebivolol products are also indicated for the treatment of chronic heart failure.

- Product information already cautions that although nebivolol does not affect glucose levels in diabetic patients, care should be taken as it may mask certain symptoms of hypoglycaemia (e.g. tachycardia, palpitations).
- An update to product information for nebivolol-containing medicines (single ingredient and fixed-dose combinations), will also reflect that beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas.
- Diabetic patients should be advised to monitor their blood glucose levels carefully.

Quetiapine: Drug-drug interaction (DDI) with serotonergic agents.

Quetiapine is indicated for the treatment of schizophrenia and bipolar disorder. Quetiapine prolonged-release tablets are also indicated for add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal responses to antidepressant monotherapy.

- Concomitant administration with other serotonergic agents, such as MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants, may result in serotonin syndrome, a potentially life-threatening condition.
- If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
- Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
- If serotonin syndrome is suspected, consider reducing the dose or discontinuing therapy, depending on the severity of symptoms.

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Clarithromycin: Drug-drug interactions (DDI) with hydroxychloroquine/chloroquine, edoxaban, ivabradine, and corticosteroids.

Clarithromycin is a macrolide antibiotic used systemically to treat various infections caused by susceptible organisms in adults and children over 6 months.

- Product information for clarithromycin-containing medicines have been updated to reflect interactions with a number of medicines.
- Ivabradine: The use of clarithromycin with ivabradine is contraindicated.
- Hydroxychloroquine/chloroquine: Clarithromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.
- Edoxaban: Caution is advised when clarithromycin is co-administered with edoxaban, particularly to patients at high risk of bleeding.
- Corticosteroids: Caution should be exercised in concomitant use of clarithromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

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

PRODUCT	SAFETY ISSUE
Veoza (fezolinetant)	Risk of drug-induced liver injury and new recommendations on monitoring of liver function before and during treatment
Risperdal/Rispone (risperidone) 1 mg/ml Oral Solution	Risk of medication errors leading to accidental overdoses in children and adolescents

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

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