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HPRA DRUG SAFETY NEWSLETTER

122ND EDITION

In this edition

Hydroxycarbamide-containing medicinal products: Potential interference with continuous glucose monitoring systems

Key Messages

- **Risk of hypoglycaemia:** Hydroxycarbamide may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems which may lead to hypoglycaemia if sensor glucose results are relied upon to dose insulin.
- **Consult with the CGM prescriber:** If CGM systems are to be used concurrently with hydroxycarbamide treatment, consult the CGM prescriber about the need to consider alternative glucose-monitoring methods.

Hydroxycarbamide-containing medicinal products are authorised in haematological and oncological indications in Ireland*.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) have recommended an update to the product information of hydroxycarbamide-containing products to include a warning about the risk of interference with CGM systems. Interference with CGM systems can lead to hypoglycaemia, if sensor glucose results are relied upon to dose insulin.

CGM systems are wearable sensors measuring glucose in the interstitial fluid based on selective oxidation at the sensor-electrode. Interference of hydroxycarbamide (also known as hydroxyurea) with CGM systems, leading to falsely elevated glucose readings, has been reported in the scientific literature.[1,2,3]

If certain continuous glucose monitoring (CGM) systems are to be used concurrently with hydroxycarbamide treatment, the CGM prescriber should be consulted about the need to consider alternative glucose monitoring methods.

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The mechanism by which hydroxycarbamide could potentially interfere with CGM systems is not proven but it is possibly directly oxidised at the electrode falsely elevating the test results. CGM systems that are available in Ireland include products from Dexcom (Dexcom G6, G7, One+), Abbott Diabetes Care (FreeStyle Libre), Medtronic (Medtronic Guardian™ Sensor), and Windzor Pharma Ltd (GlucoRx Aidex™).

A Direct Healthcare Professional Communication (DHPC) has been issued to inform healthcare professionals of these updates.

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

References

1. *Conti M, Meneghini E, Fumagalli G, Guidoni F, Bertuzzi F, Pintaudi B. Severe hypoglycemia caused by hydroxyurea interference on continuous glucose sensor integrated with advanced hybrid closed-loop system: a case report. Acta diabetologica. 2023.*
2. *Szmuilowicz ED, Aleppo G. Interferent Effect of Hydroxyurea on Continuous Glucose Monitoring. Diabetes Care. 2021;44(5):e89-e90.*
3. *Tellez SE, Hornung LN, Courter JD, Abu-El-Haija M, Nathan JD, Lawson SA, et al. Inaccurate Glucose Sensor Values After Hydroxyurea Administration. Diabetes Technol Ther. 2021;23(6):443-51*

Miconazole: Drug-drug interaction between miconazole topical formulations and warfarin

Key Messages

- **Drug-drug interaction and bleeding:** Following an EU review of available data, the EMA's PRAC has recommended a warning on the concomitant use of topical miconazole medicines and warfarin or other vitamin K antagonists, due to a drug-drug interaction. Although the product information for some miconazole medicines in Ireland already notes a potential interaction, the HPRA is reminding healthcare professionals of the risk and highlighting the new recommendations from the EMA's PRAC.
- **Healthcare professional recommendation:** Concomitant use of topical miconazole-containing products with warfarin or other vitamin K antagonists should be undertaken with caution. The anticoagulant effect should be closely monitored, and warfarin dosing adjusted as clinically appropriate.
- **Advice to patients:** Patients should be informed about the symptoms of bleeding events and advised to immediately stop treatment with miconazole and seek medical advice should they occur.

Miconazole is an antifungal agent with activity against dermatophytes, yeasts, and various other fungi, as well as antibacterial activity against certain gram-positive organisms.

Topical miconazole* is available in the EU both as a single active ingredient preparation and as part of combination products, specifically miconazole nitrate with hydrocortisone or miconazole nitrate with zinc oxide; however, only single active ingredient preparations are authorised in Ireland.

It is available in several different formulations, which in Ireland are authorised for:

- Oral use: management of superficial fungal (e.g., *Candida*) infections of the oral cavity and gastrointestinal tract in adults and paediatric patients 4 months and older.
- Topical dermatological use: treatment of fungal infections of the skin and secondary infections caused by gram-positive bacteria.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) conducted a routine periodic safety review of miconazole-containing products. The review considered published literature and spontaneous reports describing bleeding events in patients treated with warfarin concurrently with topical miconazole (dermatological and gynaecological formulations).

Miconazole is known to inhibit CYP3A4 and CYP2C9 when administered systemically, which can prolong the effects of warfarin and other vitamin K antagonists. Although systemic availability from topical miconazole application is limited and clinically relevant interactions are generally rare, the available evidence indicates that a drug–drug interaction may also occur with topical formulations.

Based on this information, PRAC considers that a causal relationship between bleeding events and a drug-drug interaction between warfarin and topical miconazole-containing medicines to be at least a reasonable possibility.

Consequently, PRAC recommended that the product information (i.e. the Summary of Product Characteristics and Package Leaflet) for topical products containing miconazole should be updated accordingly. Although some miconazole products in Ireland already carry information on this potential interaction, the HPRA is reinforcing awareness of the risk and emphasising the updated recommendations from the EMA's PRAC.

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

The importance of reports of suspected adverse reactions to pharmacovigilance

Key Messages

- **Reporting suspected adverse reactions** supports the ongoing safety monitoring of medicines in clinical use by increasing knowledge about known adverse reactions and acting as an early warning system for identifying previously unrecognised adverse reactions.
- Several options are available to report suspected adverse reactions to medicines to the HPRA, with the online reporting option accessible from the HPRA website (www.hpra.ie/report)
- Include as much information as possible; however, the lack of complete details should not prevent the submission of a report.

The HPRA sincerely thanks healthcare professionals for their ongoing commitment in reporting suspected adverse reactions. These reports play a crucial role in pharmacovigilance, helping to detect potential safety issues that may warrant further investigation. By submitting adverse reaction reports to the HPRA, healthcare professionals make a significant contribution to medicine safety and risk management. This article explains the importance of reporting suspected adverse reactions, details the reporting process, and describes what happens after a report is submitted. The HPRA pharmacovigilance team recognises the demanding nature of healthcare work and greatly appreciates the time and effort devoted to safeguarding patient safety.

The HPRA received 8598 suspected adverse reaction reports in 2025. Of the reports received in 2025, 5% were submitted by healthcare professionals. Patients can report suspected adverse reactions directly to the HPRA also and accounted for 6% of submitted reports in 2025. Marketing authorisation holders submitted 88% of suspected adverse reaction reports. A further 1% were reported by sponsors in the context of ongoing clinical trials. It is important to note that reports received by marketing authorisation holders will have been initially notified to them by healthcare professionals or members of the public.

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Why report suspected adverse reactions?

Reporting suspected adverse reactions to medicines is important. Healthcare professionals (including doctors, dentists, pharmacists and nurses) are asked to report any suspected adverse reactions observed in their practice to the HPRA's reporting system.

Information collected through the adverse reaction reporting system is essential to monitoring medicines' safety in routine clinical use. It increases knowledge about known adverse reactions and can act as an early warning system for identifying previously unrecognised safety issues. Such information is one of the tools used by the HPRA and other regulators in the ongoing safety evaluation of marketed medicines.

Whilst reports of any suspected adverse reaction are encouraged, it is of particular importance to report reactions if they relate to:

- Newly authorised medicines
- Vaccines
- Medicines used in pregnancy or breastfeeding
- Reactions experienced in paediatric or elderly populations
- Reports of addiction, dependence or experiencing withdrawal from a medicine
- Reactions experienced following an overdose, misuse or medication error
- Serious reaction to any medicine
- Medicines undergoing additional monitoring. These medicines are easily identified as they have an inverted black triangle on their product information, together with the following statement:

  ▼ This medicinal product is subject to additional monitoring.

How to report a suspected adverse reaction to the HPRA

The HPRA offers several ways to report suspected adverse drug reactions. The preferred methods are outlined below:

- An online system may be accessed via the HPRA homepage (www.hpra.ie/report)
- A downloadable report form is also available via the HPRA homepage (www.hpra.ie). It can be completed and emailed to medsafety@hpra.ie
- By email to medsafety@hpra.ie
- By letter or phone using the contact details via www.hpra.ie

What to include in suspected adverse reaction reports

To facilitate the most thorough evaluation of suspected adverse reactions, the HPRA requests that healthcare professionals include as much information as possible when submitting a report. However, please note that the non-availability of all this information should not discourage report submission.

At a minimum, there needs to be at least a single patient identifier (e.g. age, sex), a suspect medicine, a description of the suspected reaction(s) and the reporter's contact information. Please provide the brand name and batch number for biological medicinal products, including vaccines, if possible.

Additional information that would be beneficial includes:

- Information on the person who has experienced the suspected reaction, including age (or age group) and sex, and any additional available information such as weight/BMI, pregnancy/breastfeeding status, etc.
- Relevant medical history or concomitant conditions, e.g., food allergies, co-morbidities, and previous vaccine allergy.
- Any concomitant medications (including non-prescription medicines, herbal remedies, or contraceptives).

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- A description of the suspected adverse reaction, including, time to onset, clinical course and impact on the patient, any treatment administered, and outcome where known.
- Identification of the suspect medicine(s), including if known, the dose regimen and duration, and any action taken.

What happens after the report is submitted?

All suspected adverse reaction reports received are reviewed by the HPRA's pharmacovigilance officers and entered into the national pharmacovigilance database. We may contact the reporter for additional information if considered helpful to interpret the case. Reports are subsequently sent to EudraVigilance, the European Medicines Agency's (EMA) database of suspected adverse reactions, where the data are analysed to detect new safety signals. As part of ongoing medicine safety evaluation, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) evaluates safety signals from EudraVigilance and may recommend regulatory action as a result, such as updates to the product information.

In 2025, the EMA undertook a detailed review of 1,201 potential safety signals related to 995 active substances contained in centrally authorised medicines. These potential safety signals were identified following routine screening of the EudraVigilance database and other sources, such as the scientific literature.

Reports of exposure to a medicine during pregnancy are particularly important for pharmacovigilance. Pregnant women are often excluded from clinical trials, meaning that much of the available safety information comes from post-authorisation reporting. The HPRA encourages healthcare professionals to report suspected adverse reactions and any exposure to a medicine during pregnancy, even where no adverse outcome is initially apparent. Where possible, follow-up information on the pregnancy outcome at term (including normal outcomes) is also extremely valuable, as this helps regulators to better understand the benefit–risk profile of medicines used in pregnancy and to detect potential safety signals at an early stage. Such reports contribute to national and EU-wide safety monitoring through EudraVigilance and support evidence-based updates to product information.

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.

Tamoxifen: QTc interval prolongation and precaution for premenopausal women relating to bone mineral density.

Tamoxifen is indicated in the treatment of breast cancer.

QTc interval prolongation

- A new warning in product information will reflect that tamoxifen at the recommended dose may prolong the QTc interval on the electrocardiogram (ECG) especially in patients with underlying risks for QT prolongation, including patients with cardiac comorbidities or patients currently treated with other medicines known to prolong the QT interval.
- ECG and electrolyte monitoring are recommended in such patients.
- Caution is advised in case of concomitant use of tamoxifen and other medicines known to prolong the QT interval.

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Bone mineral density in premenopausal women

- Studies in premenopausal women who were treated with tamoxifen for reduction of breast cancer risk or in the management of breast cancer have reported decreases in bone mineral density.
- Premenopausal women taking tamoxifen should be advised regarding measures to maintain bone health, according to local clinical guidelines.

Netarsudil single ingredient (Rhokiinsa) and fixed dose combination with latanoprost (Roclanda): Risk of reticular epithelial corneal oedema (RECE) associated with netarsudil component.

Rhokiinsa (netarsudil) is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension. Roclanda (netarsudil with latanoprost) is indicated for the same patient cohort but for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.

- The PRAC has recommended that product information of netarsudil, both as single ingredient and in fixed dose combination products, be updated to include a risk of reticular epithelial corneal oedema (RECE).
- RECE has been reported following administration of netarsudil-containing products, particularly in patients with pre-existing corneal oedema or prior ocular surgery.
- RECE typically resolves following discontinuation of netarsudil-containing medicines.
- Patients should be advised to notify their physician if they experience decreased vision or eye pain while using netarsudil-containing products.

Vancomycin: Kounis syndrome, drug-induced liver injury (DILI) and haemolytic anaemia

Vancomycin-containing medicines are indicated in the treatment of a range of severe, potentially life-threatening infections due to susceptible gram-positive microorganisms which cannot be treated with or failed to respond to other effective, less toxic antimicrobial medicinal products, such as penicillin and cephalosporins.

- Product information updates for vancomycin-containing medicines have been recommended to reflect that cases of Kounis syndrome, increased alanine aminotransferase and aspartate aminotransferase enzymes, and haemolytic anaemia have been reported in association with vancomycin treatment.
- Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.
- Patients are warned that signs of allergic reaction, including breathing problems and chest pain, have been reported with vancomycin and to stop immediately and contact immediately their doctor or medical emergencies if they notice any of these signs.

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

PRODUCT	SAFETY ISSUE
Tegretol (carbamazepine)	Restriction of use in neonates as concentration of the excipient, propylene glycol, exceeds recommended threshold.
Remsima (infliximab)	New IV formulation (100 mg and 350 mg concentrate for solution for infusion) contains sorbitol and is therefore contraindicated in patients with hereditary fructose intolerance.
Mykronor (noradrenaline)	Noradrenaline, Mykronor 5 µg/mL, solution for injection/infusion - potential risk of medication errors
Ixchiq (Chikungunya vaccine (live-attenuated))	PRAC warns about known risk of aseptic meningitis with chikungunya vaccine Ixchiq

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

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