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HPRA DRUG SAFETY NEWSLETTER

116TH EDITION

In this edition

Chlorhexidine: Inadvertent ocular exposure during surgical site preparation

Key Message

- Despite the use of eye protection, serious corneal injuries, sometimes requiring transplants, have been reported following inadvertent eye exposure to chlorhexidine-containing solutions used for head and neck surgical site preparation. This occurs when the solution spreads beyond the intended area.
- Extreme care should be taken when applying chlorhexidine-containing medicines used during head and neck surgical site preparation to ensure it does not spread beyond the intended area and reach the eyes.
- Particular care is needed with anaesthetised patients, as they cannot immediately report ocular exposure.

Chlorhexidine-containing products* are authorised for various indications in Ireland and across EU Member States, including skin disinfection before medical procedures.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency has recommended updating the product information** for chlorhexidine-containing medicines indicated for skin disinfection and intended for cutaneous use. This follows a review of evidence showing that accidental ocular exposure to chlorhexidine has occurred during head and neck surgical site preparation. The inadvertent ocular exposure has been reported, in some cases, to result in persistent corneal injury and visual impairment, potentially requiring corneal transplant. This is despite taking eye protective measures and due to the migration of solution beyond the intended surgical preparation area.

The revised product information will include a warning stating that extreme care should be taken during surgical site preparation when applying chlorhexidine medicines to ensure that the chlorhexidine product does not migrate beyond its intended application site into the eyes.

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Particular care should be taken in anaesthetised patients who cannot report ocular exposure immediately. If chlorhexidine products come into contact with the eyes, they should be washed out promptly and thoroughly with water, and advice from an ophthalmologist should be sought.

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

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

Availability of Educational Materials for Valproate (Epilim▼) and Topiramate (Topamax▼)

The HPRA wishes to highlight the availability of educational materials to manage potential risks associated with the antiepileptic drugs valproate (Epilim▼) and topiramate (Topamax▼). The HPRA has recently approved the distribution of these educational materials to target groups of healthcare professionals by the respective pharmaceutical companies.

Healthcare professionals are reminded that the official approved product information for all antiepileptic drugs includes advice on use in pregnancy and lactation (section 4.6 of the summary of product characteristics). Educational materials, when available, should be used in conjunction with the summary of product characteristics and package leaflet. Product information and educational materials are accessible on www.hpra.ie using the 'Find a medicine' search function. The HPRA has also previously published a special edition of its Drug Safety Newsletter (DSN 106) summarising the available evidence for several of these medicines.

Valproate (Epilim▼) educational materials

Male patients

Educational materials for male patients have been developed to support the implementation of new precautionary measures for valproate use in male patients in clinical practice*. These include:

- A new patient guide which should be provided to all male patients treated with valproate. This guide provides information regarding the potential risk of neurodevelopmental disorders (NDDs) in children of fathers treated with valproate in the three months prior to conception.
- An updated healthcare professional guide that includes a dedicated section on male patients to inform healthcare professionals about the potential risk of NDDs and advice to provide to male patients and their female partners.
- An updated patient card (attached to the outer packaging) that includes information relating to the potential risk of NDDs in children of fathers treated with valproate in the three months prior to conception. Whilst the packaging is updated, copies of the updated patient card have been made available to provide each time valproate is dispensed.

* *For more information, see the HPRA's Drug Safety Newsletter 115 and the Direct Healthcare Professional Communication.*

Female patients

Existing educational materials for girls and women of childbearing potential to support implementing the pregnancy prevention programme (known as 'prevent') have been revised. The updates are in light of a recent EU survey evaluating the effectiveness of risk minimisation measures for valproate, following which the European Medicines Agency (EMA) recommended updates to the healthcare professional and patient educational materials. The updates aim to further reinforce the understanding of the risks associated with valproate use during pregnancy, including teratogenic effects and NDDs, while ensuring adherence to prescribing conditions and the pregnancy prevention programme. There have been no changes to the safety information nor the measures advised as part of 'prevent' within the guides.

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- The female patient guide has been revised for better readability, incorporating flow charts and illustrations to aid understanding.
- The healthcare professional guide has undergone a significant restructuring. The guide is now organised according to the healthcare professional's role and the specific indication for valproate use, allowing for improved understanding, visualisation, and navigation.
- Other tools that are available include the annual risk acknowledgement form and a poster and shelf barker for use in pharmacies.

Patient-facing materials are accessible through the following QR code, which is also approved as part of the package leaflet.

All educational materials and additional background information are available on the HPRA's valproate special topics page.

qr.epilimandme.ie

Topiramate (Topamax▼) educational materials

A pregnancy prevention programme has been introduced for topiramate, following an EU review of the risks associated with its use in pregnancy (Direct Healthcare Professional Communication and DSN113). New educational materials have been developed to support the implementation of measures to mitigate the risk of topiramate exposure during pregnancy. These educational materials have been recently distributed to target groups of healthcare professionals by the pharmaceutical company, following approval by the HPRA.

- A new patient guide has been developed to help inform patients about the risks associated with topiramate use during pregnancy. The guide should be provided to girls and women of childbearing potential who are prescribed topiramate.
- A new healthcare professional guide has been developed to provide comprehensive instructions on implementing the pregnancy prevention programme.
- A new annual risk awareness form has been developed. This form should be discussed and completed by the doctor with all female patients of childbearing potential treated with topiramate at the start of treatment (or when menarche is reached), each subsequent annual visit, when planning a pregnancy, or if pregnancy occurs.
- A new patient card has been developed. Pharmacists should ensure that female patients of childbearing potential receive a card each time topiramate is dispensed. This card will also be included in the Topamax▼ product packs in the future. In the interim, the pharmaceutical company has provided hard copies of patient cards, available on the HPRA webpage.

For further information on topiramate, including the product information and educational materials, please see the HPRA's dedicated topiramate webpage or use the 'Find a medicine' search box and enter 'Topamax'.

Patients may access all patient-facing material through the following QR code which is also, approved as part of the package leaflet.

All educational materials and additional background information are available on the HPRA's topiramate special topics webpage.

www.topamaxandme.ie

Valproate and topiramate information session

The HPRA hosted an information session in March 2024. A recording of the session has been uploaded to HSelanD.

Instructions on how to access the recording in HSeLanD have been provided below.

- Log into HSeLanD and click the Hubs and Resources section at the top of the page.
- From here, click into the Discovery Zone tile (view the Hub)
- Type into the search bar' Important safety updates relating to topiramate and valproate medicines (March 2024)'
- Here you will be able to view the material.

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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 check the HPRA or EMA websites regularly for current product information concerning medicines.

Gentamicin (systemic use): Increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial DNA mutations

Gentamicin is indicated in bacteraemia, urinary tract infections, chest infections, severe neonatal infections and other serious systemic infections due to susceptible organisms in adults and children including neonates.

- Product information for gentamicin-containing products has been updated to reflect an increased risk of ototoxicity in patients with mitochondrial DNA mutations.
- This is particularly associated with the nucleotide substitution 1555 A to G in the 12S rRNA gene.
- The risk is present even if aminoglycoside serum levels are within the recommended range during treatment.
- In patients with a maternal history of relevant mutations or aminoglycoside-induced deafness, alternative treatments or genetic testing before administration should be considered.

Pregabalin: Suicidal ideation and withdrawal symptoms

Pregabalin is indicated in adults for the treatment of peripheral and central neuropathic pain, the treatment of Generalised Anxiety Disorder (GAD), and as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

- Product information for pregabalin will be updated to include suicidal ideation as a withdrawal symptom that has been reported following discontinuation of treatment.
- Withdrawal symptoms have been observed after discontinuation of short- and long-term treatment. If pregabalin treatment is to be discontinued, it is recommended that it is done gradually over a minimum of one week.
- Patients should be advised to contact their doctor if they experience withdrawal symptoms outlined in the product information (insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, suicidal ideation, pain, convulsion, hyperhidrosis and dizziness).

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

PRODUCT	SAFETY ISSUE
CD19- or BCMA-directed CAR T-cell therapies	Risk of secondary malignancy of T-cell origin
17-hydroxyprogesterone caproate	European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) recommends suspension of the marketing authorisation
Glatiramer acetate	Anaphylactic reactions may occur months up to years after treatment initiation.

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The Importance of Reports of Suspected Adverse Reactions to Pharmacovigilance

Key Message

- 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 would like to thank healthcare professionals for their continued commitment to reporting suspected adverse reactions. These reports are invaluable to pharmacovigilance efforts, as they help identify potential safety signals that may require further investigation. By taking the time to report adverse reactions to the HPRA, healthcare professionals contribute significantly to patient safety. This article outlines why and how to report suspected adverse reactions and what happens after a report is made. The HPRA pharmacovigilance team understands the demanding nature of healthcare work and is grateful for the time and effort dedicated to reporting safety concerns.

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 triangle on their product information, together with the following statement: ▼ This medicinal product is subject to additional monitoring.

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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 on the HPRA homepage (www.hpra.ie/report). 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, gender), 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, co-morbidities, 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).
- 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 staff 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.

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

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