



Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.



NICE has accredited the process used by the MHRA to produce Drug Safety Update guidance. More information on accreditation can be viewed on the [NICE website](https://www.nice.org.uk/accreditation).

To subscribe to monthly email alerts of Drug Safety Update see: <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/email-signup>

This month, we have advice for healthcare professionals when switching patients between different metolazone preparations – see page 2.

On page 6, we describe the risk of accidental exposure of children to testosterone from a topical testosterone gel used by their parents and caregivers and provide advice to avoid this.

On page 9, we ask healthcare professionals to be vigilant to adverse incidents involving software, apps, and artificial intelligence (AI) as medical devices and to report incidents to us via the Yellow Card scheme.

Next, on page 11 we summarise recent advice relating to COVID-19 vaccines and medicines published since the December 2022 issue of Drug Safety Update. And on page 12, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines and medical devices.

If you have been forwarded this issue of Drug Safety Update, subscribe directly via [our website](#).

Xaqua (metolazone) 5mg tablets: exercise caution when switching patients between metolazone preparations

Prescribers and dispensers should use caution if switching patients between different metolazone preparations as the rate and extent of absorption of metolazone are formulation dependent. This can impact the bioavailability of the product. Follow good practice in prescribing medicines by considering the licensed formulation (Xaqua) in preference to unlicensed imported metolazone preparations in new patients. The product information for Xaqua has been updated to clarify that references to comparative bioavailability with other metolazone products relate specifically to Metenix and not to any other metolazone preparations.

Advice for healthcare professionals:

- healthcare professionals have expressed concerns about switching patients between metolazone preparations due to potential differences in the bioavailability and dosing instructions between products
- follow good practice in prescribing medicines by considering the licensed formulation (Xaqua) in preference to unlicensed imported metolazone preparations in new patients
- assess individual patient factors before switching patients from unlicensed imported metolazone products to Xaqua
- consider dose adjustment, due to potential differences in bioavailability, at the time of switching from unlicensed imported metolazone products to Xaqua
- monitor patients to assess the clinical impact of the switch – monitoring should be done on an individual basis after an assessment of the patient's risk, and could include assessment of blood pressure, electrolytes and degrees of oedema and breathlessness
- do not divide Xaqua tablets into quarters – when it is necessary to split tablets, this should be only into halves using the tablet score-line
- tell the patient if their prescribed dose means that they have to split their Xaqua tablet and ensure that this is documented clearly on the medication label and in medication records where appropriate
- prescribe and supply metolazone by product name and document this clearly, especially for transfers of care
- report suspected adverse drug reactions associated with metolazone on a [Yellow Card](#)

Advice for healthcare professionals to give to patients and carers:

- if you currently use an imported unlicensed metolazone product your doctor will assess your suitability to be switched to Xaqua
- do not use different metolazone preparations at the same time
- be aware of the brand of metolazone you are prescribed and ask your healthcare professional about any changes they make to your prescription
- be aware if your dose of metolazone means the tablets need to be split and if these will be dispensed to you already split or if you need to split the tablets yourself
- be aware of the dosing instructions for your metolazone tablets – switching to Xaqua may require you to change from taking your tablets once a day to alternate days
- you may need additional blood tests and checks of your blood pressure and weight when you are switched to Xaqua
- be aware of the warning signs and symptoms of electrolyte imbalance which could occur on switching metolazone products and contact a healthcare professional if you experience these (symptoms include: dry mouth; thirst; weakness; lethargy; drowsiness; restlessness; muscle pains or cramps; muscle fatigue; low blood pressure; low urine volume; racing heartbeat and gastrointestinal disturbances such as nausea and vomiting)
- be aware of the signs and symptoms you might experience if the dose of your medication is too low and contact a healthcare professional if you experience these (symptoms include increasing breathlessness, weight gain and worsening swelling of the extremities)
- do not stop your treatment without discussing with your doctor first
- if you experience any side effects, please [report them to the Yellow Card scheme](#)

About metolazone

Metolazone is a sulphonamide with thiazide-like diuretic properties indicated for the treatment of hypertension and oedema. Treatment is usually initiated and monitored by specialists.

In recent years, metolazone was supplied to the UK as an unlicensed import from other countries in which it held a licence. As such, it was only prescribed to patients when clinically necessary. In February 2021, Renascence Pharma Ltd received UK marketing approval for a new metolazone product: Xaqua 5 milligram (mg) Tablets.

The [Xaqua Summary of Product Characteristics](#) advises a dose of 2.5mg to 5mg per day for the licensed indications of hypertension and oedema related to congestive heart failure or kidney disease. These doses may be adjusted according to the individual response of the patient.

Healthcare professionals have expressed concerns to the MHRA with respect to switching patients between metolazone preparations due to potential differences in the bioavailability and dosing instructions between Xaqua and unlicensed imported metolazone preparations.

The Specialist Pharmacy Services (SPS) recently published [guidance to healthcare professionals on the differences between metolazone preparations and safety considerations](#) (published 7 September 2022 and updated 13 September 2022).

The MHRA sought independent advice from Expert Advisory Groups of the [Commission on Human Medicines](#), which recommended that the Marketing Authorisation Holder for Xaqua circulate a [letter to healthcare professionals](#) to reinforce key messages about initiating metolazone treatment or switching to Xaqua. In addition, the product information for Xaqua has been updated to clarify that references to comparative bioavailability with other metolazone products relate specifically to Metenix (a formerly licenced product, which was withdrawn in the UK in March 2012 for commercial reasons) and not to any other metolazone preparations. Metenix is the only product for which there is comparative bioavailability data.

Advice on initiating metolazone

Specialists are advised to prescribe the licensed product Xaqua when initiating metolazone treatment rather than an unlicensed imported metolazone preparation.

Currently, there is no national UK guidance on the use of metolazone. However, local guidance may be available in the form of shared care, prescribing and monitoring and/or clinical specialty guidelines.

Individual patient factors should be considered before initiating metolazone treatment. These include:

- the indication, co-morbidities and concomitant treatments
- the patient's degree of fragility and ability to tolerate potential fluid and electrolyte imbalances
- the risk of side effects from excessive or sub-therapeutic dosing
- what monitoring arrangements are in place
- the patient's ability to manage the handling of partial tablets (halving) or alternate day dosing regimens
- the patient's understanding of the treatment and when to contact a healthcare professional

Arrangements for clinical monitoring should be made on an individual basis after an assessment of the individual clinical risk. Relevant parameters for monitoring include blood urea, electrolytes and creatinine, blood pressure and weight. The frequency of monitoring should be based on the individual patient.

Advice on switching to Xaqu

Specialists should manage the switching of patients already taking an unlicensed imported metolazone product to Xaqu. The individual patient factors listed in the previous section should be considered. Arrangements for monitoring should be made on an individual basis after an assessment of the individual clinical risk.

If switching to Xaqu is appropriate, the dose of metolazone provided as Xaqu may need to be adjusted to take account of individual patient factors, and the difference in bioavailability between Xaqu and the metolazone preparation being replaced (where that information is available).

In the absence of comparative bioavailability data to inform a dose recommendation, an option may be to reduce the dose by half (from unlicensed metolazone to Xaqu) and/or adjust the frequency of dosing of Xaqu (for example, from unlicensed metolazone daily to Xaqu on alternate days). The dose can then be titrated upwards under increased monitoring, if necessary.

Advice on continuing treatment with unlicensed metolazone

If switching is not considered clinically appropriate it should be highlighted to the patient precisely which metolazone preparation they are receiving (including manufacturer, brand name (if available) and dose). The prescription and supply of metolazone should be product-specific and documented clearly, especially for transfers of care.

Report suspected drug reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the [Yellow Card scheme](#). Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the [Yellow Card website](#)
- the Yellow Card app; download from the [Apple App Store](#) or [Google Play Store](#)
- some clinical IT systems for healthcare professionals (EMIS, SystemOne, Vision, MiDatabank, and Ulysses)

When reporting please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using the [dedicated Coronavirus Yellow Card reporting site](#) or the Yellow Card app. See the MHRA website for the [latest information on medicines and vaccines for COVID-19](#).

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Topical testosterone (Testogel): risk of harm to children following accidental exposure

Premature puberty and genital enlargement have been reported in children who were in close physical contact with an adult using topical testosterone and who were repeatedly accidentally exposed to this medicine. To reduce these risks, advise patients to wash their hands after application of topical testosterone, cover the application site with clothing once the product has dried, and wash the application site before physical contact with another adult or child.

Advice for healthcare professionals:

- when prescribing topical testosterone, inform patients of the potential consequences if it is accidentally transferred to other people
- inform patients that accidental transfer can lead to increased blood testosterone levels in the other person
- advise patients of the possible effects should accidental exposure occur in adult women (facial and/or body hair growth, deepening of voice, changes in menstrual cycle) or children (genital enlargement and premature puberty, including development of pubic hair)
- counsel patients on methods to reduce the risks of accidental exposure, including washing their hands with soap and water after application, covering the application site with clean clothing (such as a t-shirt) once the gel has dried, and washing the application area with soap and water before physical contact with another person
- encourage patients to be vigilant about implementing measures to minimise risk, to be alert for signs of accidental exposure, and to seek medical advice if accidental exposure is suspected
- report suspected adverse drug reactions associated with topical testosterone on a [Yellow Card](#)

Advice for healthcare professionals to provide to patients:

- topical testosterone products are used for testosterone replacement. When using these products on your skin, you must take care that the testosterone product is not accidentally transferred onto the skin of someone else
- if the testosterone in the product is accidentally transferred to someone else through physical contact, it can lead to increased blood testosterone levels in the other person. It can cause facial and body hair growth, deepening of voice and changes in the menstrual cycle of women, or accelerated height, genital enlargement, and early puberty (including development of pubic hair) in children

- the following precautions can reduce the risk of accidentally transferring testosterone from the patient's skin to another person:
 - after applying the product, wash your hands with soap and water
 - once the product has dried, cover the application site with clean clothing (such as a t-shirt)
 - before physical contact with another person (adult or child), wash the application site with soap and water after the recommended time period following application has passed

About topical testosterone

Topical testosterone products are gels or creams applied directly to the skin. They are authorised to replace testosterone in men who do not produce sufficient natural testosterone; a condition known as hypogonadism. It acts in the same way as the testosterone that is produced in the body, which is responsible for the development of genitals and maintaining sexual characteristics (deepening of voice, hair growth, and sex drive). These products are also used outside of the licence for a range of conditions, including for peri/post-menopausal symptoms in women.

Accidental exposure to topical testosterone products

If this product is repeatedly accidentally transferred to another person through physical contact, it can increase their blood testosterone levels. This may result in possible side effects (for example, growth of facial and/or body hair, deepening of the voice, irregular menstrual cycles in women, and premature puberty and genital enlargement in children).

Reports of accidental exposure of topical testosterone to children

The MHRA received a report of a child who was repeatedly accidentally exposed to the topical testosterone product that their parent was using, resulting in increased growth and genital enlargement. It was confirmed through clinical investigations that the child had increased testosterone in their blood and that the topical testosterone product was the source of the testosterone. There are also literature reports and non-UK reports of premature puberty and genital enlargement in children who were repeatedly accidentally exposed to a topical testosterone product via transfer from an adult with whom they were in close contact.

The risk was reviewed by the [Paediatric Medicines Expert Advisory Group of the Commission on Human Medicines](#), which recommended that a specific paediatric warning be added to the product information for topical testosterone products.

We have requested that the manufacturers of topical testosterone products update the Summary of Product Characteristics and the Patient Information Leaflet. These updates will provide warnings about accidental exposure to children and set out the precautions concerning washing the application site before physical contact with another person (adult or child). A specific warning will be included about the risk of accidental testosterone transfer to children.

Report any suspected adverse drug reactions

Please continue to report suspected adverse drug reactions via the [Yellow Card scheme](#). Your report will help us safeguard public health.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the [Yellow Card website](#)
- the Yellow Card app; download from the [Apple App Store](#) or [Google Play Store](#)
- some clinical IT systems for healthcare professionals (EMIS, SystemOne, Vision, MiDatabank, and Ulysses)

When reporting, please provide as much information as possible, including information about batch numbers, medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Report suspected side effects to medicines, vaccines, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment using the [dedicated Coronavirus Yellow Card reporting site](#) or the Yellow Card app. See the MHRA website for the [latest information on medicines and vaccines for COVID-19](#).

The [public consultation](#) on how the MHRA communicates medicines and medical devices safety information to healthcare professionals is now open. The consultation is a unique opportunity to influence future MHRA safety communications and safety reporting systems so please encourage all healthcare professionals to complete the survey. The deadline for responses has been extended to 11.45pm on Tuesday 31 January.

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Electronic Prescribing and Medicines Administration Systems: report adverse incidents on a Yellow Card

We ask healthcare professionals to be vigilant to adverse incidents involving software, apps, and artificial intelligence (AI) as medical devices and to report incidents to us via the Yellow Card scheme.

Advice for healthcare professionals:

- be alert for potential errors occurring when using Electronic Prescribing and Medicines Administration Systems (ePMAS) which may lead to patient harm, especially errors involving the dosing of medicines or vaccines
- ePMAS and other software, apps and artificial intelligence intended to be used for a medical purpose are likely to be medical devices and any adverse incidents involving these devices should be reported to the MHRA's Yellow Card scheme
- use the new [digital Yellow Card](#) report form to inform us about adverse incidents involving software as a medical device

Background

The term 'medical device' covers a broad range of products that are used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or disability. Electronic Prescribing and Medicines Administration Systems (ePMAS) are used widely across the UK healthcare system and may qualify as medical devices. Where necessary, they should be CE or UKCA marked to demonstrate conformity with the [9UK Medical Device Regulations \(2002\)](#).

The MHRA has been undertaking work with manufacturers of these ePMAS devices following the publication of the Healthcare Safety Investigations Board (HSIB) report on [weight-based medication errors in children](#). This review was conducted following a case in which a child received a 10-times overdose of an anticoagulant medicine due to errors in the prescription, dispensing and administration processes. The HSIB noted that, although ePMAS are considered an effective way to reduce medication errors they may cause new technology-related errors.

We ask for any potential errors with ePMAS to be reported to us, to help us work with manufacturers to reduce these risks.

Report incidents on a Yellow Card

ePMAS products and other software, apps and Artificial Intelligence intended to be used for a medical purpose are likely to be medical devices. The MHRA has developed a version of the [digital Yellow Card](#) report form for suspected adverse incidents involving software as a medical device. Please select 'standalone software and medical device apps' in the drop-down menu to access the software medical device form.

There are specific arrangements for healthcare professionals to follow in each of the devolved administrations.

Healthcare professionals should report incidents to:

- in England and Wales to the [Yellow Card scheme](#) or via the Yellow Card app
- in Scotland to [NHS National Services Scotland online incident reporting system](#) and their local incident recording system
- in Northern Ireland to the [Northern Ireland Adverse Incident Centre](#) and their local incident recording system

Healthcare professionals should continue to report suspected adverse drug reactions to the Yellow Card scheme. Patients and caregivers can also report suspected adverse drug reactions and medical device incidents directly to the Yellow Card scheme.

The [public consultation](#) on how the MHRA communicates medicines and medical devices safety information to healthcare professionals is now open. The consultation is a unique opportunity to influence future MHRA safety communications and safety reporting systems so please encourage all healthcare professionals to complete the survey. The deadline for responses has been extended to 11.45pm on Tuesday 31 January.

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COVID-19 vaccines and medicines: updates for January 2023

Summaries of Yellow Card reporting

We continue to publish the summaries of the [Yellow Card reporting for the COVID-19 vaccines](#) being used in the UK. The report summarises information received via the Yellow Card scheme and will be published regularly to include other safety investigations carried out by the MHRA under the [COVID-19 Vaccine Surveillance Strategy](#).

The MHRA has revised the format of the [Summary of Yellow Card reporting](#) to focus on the COVID-19 vaccines administered from the beginning of the Autumn 2022 booster campaign. Any new assessments or safety issues regarding vaccines used in the primary and initial booster campaigns will also be included in this record, however previous and known information on these vaccines will remain available as a record only and can be viewed in an [archived form on our website](#). Yellow Card reports received via the scheme across all vaccines will be updated and reflected in the [COVID-19 vaccine reports](#).

The MHRA has begun implementing a new enhanced format of data visualisations. This enables us to provide improvements in format, accessibility and data protection, while also providing more data than has been published previously. Since December 2022, [COVID-19 vaccine reports](#) have replaced the previous Vaccine Analysis Prints (VAPs).

Other recent MHRA updates on COVID-19 vaccines and medicines

We have also recently:

- published our [Public Assessment Report on the Pfizer/BioNTech bivalent vaccine](#) - Comirnaty Original/Omicron BA.4-5
- updated the [Pfizer Omicron BA.1 and BA.4-5 SmPC and PIL documents](#)
- [authorised VidPrevtyn Beta, the COVID-19 vaccine developed by Sanofi](#), after finding it meets the MHRA's acceptable standards of safety, quality and effectiveness

See [guidance on COVID-19 for all our latest information](#), including after publication of this article. We previously included summaries of latest COVID-19 information, including in the [October 2022](#), [November 2022](#) and [December 2022](#) issues of Drug Safety Update.

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Letters and medicine recalls sent to healthcare professionals in December 2022

Letters

In December 2022, the following letters were sent or provided to relevant healthcare professionals:

- [Xaqua \(metolazone\) 5mg tablets: differences with other metolazone preparations and safety considerations required when switching patients](#) – see [article in January 2023 Drug Safety Update](#)
- [Lagevrio 200 mg hard capsules \(molnupiravir\) – Extended Use Beyond Labelled Expiry Date](#)
- [Kaftrio 75mg/50mg/100mg \(ivacaftor/tezcaftor/elexacaftor\) and Kalydeco 50mg, 75mg and 150mg film coated tablets \(ivacaftor\): Temporary Supply of stock to UK\(NI\) with blue box referencing Ireland only](#)
- [ONUREG 300mg Film-coated Tablets \(oral azacitidine\): Interim Supply of Northern Ireland \(NI\) Stock to Mitigate Supply Disruption](#)
- [Incorrectly labelled bottles of Bylvay \(odevixibat\) 1200 mcg Hard Capsules \(PLGB 36216/0004\) batch W067208E – Caution in Use](#)
- [Lymphoseek \(tilmanocept\) 50 micrograms kit for radiopharmaceutical preparation: temporary 17-month extension of shelf life of LOT 347446](#)
- [Discontinuation of Fragmin \(Dalteparin Sodium\) 10,000IU/1 ml ampoule \(PL 00057/977\)](#)

Medicine Recalls and Notifications

In December 2022, recalls and notifications for medicines were issued on:

[Class 4 Medicines Defect Information: ADVANZ PHARMA, MacroBID 100mg Prolonged-Release Capsules, EL \(22\)A/50](#). Issued 5 December 2022. Certain batches (see link for details) of MacroBID 100mg Prolonged-Release Capsules have been packed with the incorrect Patient Information Leaflet (PIL). There is no risk to product quality and efficacy, therefore the affected batches are not being recalled. Healthcare professionals are advised to exercise caution when dispensing the affected batches and to provide patients with a copy of the Summary of Product Characteristics (SmPC).

[Class 4 Medicines Defect Information: Galderma \(U.K.\) Limited, Etrivex 500 micrograms/g Shampoo, EL \(22\)A/51](#). Issued 6 December 2022. The patient information leaflet (PIL) packaged in specific batches (see link for details) of Etrivex Shampoo is missing safety information. There is no risk to product quality, therefore the affected batches are not being recalled. Healthcare professionals are advised to exercise caution when dispensing the affected batches. Where possible, provide an updated copy of the PIL (link provided in letter) to the patient and remind them to read the leaflet in its entirety before using the medicine.

[Class 4 Medicines Defect Information: Galderma \(U.K.\) Limited, Epiduo 0.1% / 2.5% gel \(45 g\), EL \(22\)A/52](#). Issued 19 December 2022. The Patient Information Leaflet (PIL) packaged in some batches of Epiduo 0.1% / 2.5% gel contains outdated safety information regarding pregnancy. There is no risk to product quality. Healthcare professionals are advised to exercise caution when dispensing the affected batches (see link for details) and, where possible, to provide an updated copy of the PIL and remind the patient to read the leaflet in its entirety before using the medicine.

The [public consultation](#) on how the MHRA communicates medicines and medical devices safety information to healthcare professionals is now open. The consultation is a unique opportunity to influence future MHRA safety communications and safety reporting systems so please encourage all healthcare professionals to complete the survey. The deadline for responses has been extended to 11.45pm on Tuesday 31 January.

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