



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/drug-safety-update>

In our first article, we highlight the new safety and educational materials to be used to support measures for men and women under 55 years of age taking valproate. These include updated healthcare professional guide, patient guide, annual risk acknowledgement form, risk acknowledgement form for male patients starting valproate, patient card, pharmacy poster and warning stickers.

Second, we advise healthcare professionals that systemic fluoroquinolones must now only be prescribed when other commonly recommended antibiotics are inappropriate. This follows a review by the MHRA which looked at the effectiveness of current measures to reduce the identified risk of disabling and potentially long-lasting or irreversible side effects.

Third, we inform healthcare professionals of a dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl ester medicines (Omacor/Teromeg 1000mg capsules).

Our final article provides a summary of recent letters 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](#).

Valproate (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age

New safety and educational materials have been introduced for men and women and healthcare professionals to reduce the harms from valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the risk of impaired fertility in males. These safety and educational materials support the new regulatory measures announced in the [National Patient Safety Alert](#).

Healthcare professionals should review the new measures and materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate.

We are also reviewing data highlighted in [Drug Safety Update August 2023](#), which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. As a precaution we advise male patients who are planning a family within the next year, to discuss treatment options with a healthcare professional.

Advice for healthcare professionals:

- valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available
- at their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate, however subsequent annual reviews will only require one specialist
- general practice and pharmacy teams should continue to prescribe and dispense valproate and if required offer patients a referral to a specialist to discuss their treatment options. Valproate should be [dispensed](#) in the manufacturer's original full pack
- report suspected adverse drug reactions associated with valproate on a [Yellow Card](#)

Advice for healthcare professionals to give to patients and the public:

- do not stop taking valproate without advice from a specialist. This is because epilepsy or bipolar disorder may worsen without treatment
- if you are on valproate, please attend any offered appointments to discuss your treatment plan and talk to a healthcare professional if you are concerned
- consult the [Patient Information Leaflet](#) and new [Patient Guide](#) for information about the risks of valproate – see also the [MHRA information page](#) for resources

- as a precaution, male patients who are planning a family within the next year should speak to a healthcare professional about their treatment options

Valproate treatment and new safety measures

Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are followed.

In 2022, the [Commission on Human Medicines](#) (CHM) reviewed the latest data on the safety of valproate. The CHM heard from patients and other representatives about how valproate was being used and how the risks were currently managed. The CHM noted that data from the [Medicine and Pregnancy Registry](#) showed that pregnancies in England continue to be exposed to valproate.

The CHM also considered other known risks of valproate, including the risk of impaired male fertility. The CHM considered pre-clinical data on possible transgenerational risks with prenatal exposure, as well as data from studies in juvenile and adult animals suggesting adverse effects on the testes. There are currently limited data available on many of these risks in humans and further studies are planned. However, the CHM noted many patients receiving valproate have other therapeutic options with fewer potential reproductive harms.

On 28 November 2023, MHRA issued a [National Patient Safety Alert](#) to instruct Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland) to prepare for the new risk minimisation measures by 31 January 2024. The new safety and educational materials support these measures.

Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP).

The CHM will consider further recent registry [data](#) which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. In the study, around 5 children in 100 born to fathers treated with valproate around conception were diagnosed with a neurodevelopmental disorder. This is compared to 3 in 100 children whose fathers were taking lamotrigine or levetiracetam around conception (two other anti-seizure medicines). As a precaution male patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options.

See the [MHRA Public Assessment Report](#) and [MHRA website](#), which will be added to in the coming weeks and months. The [MHRA review of antiepileptic drugs in pregnancy](#) should also be consulted.

New Regulatory Safety and Educational Materials

To support the implementation of the new measures for valproate, the following safety and educational materials are being made available:

- **Updated [Healthcare Professional Guide](#):** Provides updated information for healthcare professionals on the risks of valproate in pregnancy and the risks for male patients, the new conditions for valproate prescribing and key points for patient discussions.
- **Updated [Patient guide](#):** Provides those taking valproate (or their parent, caregiver, or responsible person) with updated information on the risks of valproate in pregnancy and the risks to male patients and what they need to do.
- **Updated [Annual Risk Acknowledgement Form](#):** For female patients starting valproate and at annual review. Used to support and record the discussion between the patient and specialist prescriber on the risks associated with valproate in pregnancy and to record the decision of the countersigning specialist. At subsequent annual reviews only one specialist is required.
- **New [Risk Acknowledgement Form for male patients starting valproate](#):** Used to support and record the discussion between the patient and specialist prescriber of the risks associated with valproate in males when starting treatment with valproate and to record the decision of the countersigning specialist. This is only to be completed at initiation of valproate.
- **[Patient card](#):** Provides key information for female patients receiving valproate on contraception and pregnancy prevention.
- **[Pharmacy poster](#):** Provides important actions for pharmacists dispensing valproate to female patients.
- **[Warning stickers](#):** To be added to packaging of medicine in exceptional circumstances where the original pack cannot be dispensed.

The updated product information and safety and educational materials are available on the [MHRA website](#) and the [electronic Medicines Compendium](#). Links to the patient guide and patient card are also available via a QR code provided in the Patient Information Leaflets for Epilim and Depakote. The Marketing Authorisation Holders are sending a letter to healthcare professionals to support these changes with the hard copies of the materials which will begin distribution next week. On receipt of the new materials, healthcare professionals should discard previous versions of the valproate materials.

Further materials to support discussions with patients

Patients on valproate must be fully informed of the potential risks and counselled on their treatment options at the time of initial prescribing and at all subsequent reviews.

We ask clinicians to use appropriate individualised language when discussing the implications of taking valproate with patients and their caregivers.

The safety and educational materials should be used alongside other resources to support patients making decisions about valproate and other treatments for epilepsy and bipolar disorder. These include patient support tools, such as those published by the [NHS](#) and guidelines produced by the [Association of British Neurologists](#).

Report suspected reactions on a Yellow Card

Valproate is a black triangle medicine, and all suspected adverse reactions should be reported via the Yellow Card scheme. Reports can be made of suspected reactions experienced at any time, including historic adverse experiences with medicines.

Please include in the report as much detail as possible, particularly if a side effect continued or started after treatment was stopped. Information about medical history, any concomitant medication, onset timing, treatment dates, and product brand name should also be included.

Report to the Yellow Card scheme electronically using:

- the [Yellow Card scheme 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)

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Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate

Systemic fluoroquinolones must now only be prescribed when other commonly recommended antibiotics are inappropriate. This follows a review by the MHRA which looked at the effectiveness of current measures to reduce the identified risk of disabling and potentially long-lasting or irreversible side effects.

Advice for healthcare professionals:

- systemic (by mouth, injection, or inhalation) fluoroquinolones can cause long-lasting (up to months or years), disabling and potentially irreversible side effects, sometimes affecting multiple body systems and senses
- the UK indications for systemic fluoroquinolones have been updated so they must only be used in situations when other antibiotics, that are commonly recommended for the infection, are inappropriate
- situations in which other antibiotics are considered to be inappropriate and where a fluoroquinolone may be indicated are where:
 - there is resistance to other first-line antibiotics recommended for the infection
 - other first-line antibiotics are contraindicated in an individual patient
 - other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped
 - treatment with other first-line antibiotics has failed
- this goes further than previous measures which set out that fluoroquinolones should not be prescribed for non-severe or self-limiting infections, or non-bacterial conditions, for example non-bacterial (chronic) prostatitis. These measures are still in place.
- as a reminder, patients should be advised to stop fluoroquinolone treatment at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy and central nervous system effects, and to contact their doctor immediately
- refer to MHRA's sheet for patients ([regular print](#) or [large print](#)) for further advice
- remain alert to the risk of suicidal thoughts and behaviours with use of fluoroquinolone antibiotics. A reminder about these risks was published in the [September 2023 issue](#) of Drug Safety Update.
- as a reminder of advice published in our [August 2023 issue](#) of Drug Safety Update:
 - avoid fluoroquinolone use in patients who have previously had serious adverse reactions with a quinolone antibiotic (for example, nalidixic acid) or a fluoroquinolone antibiotic
 - prescribe fluoroquinolones with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants, because they are at a higher risk of tendon injury

- avoid coadministration of a corticosteroid with a fluoroquinolone since this could exacerbate fluoroquinolone-induced tendinitis and tendon rupture
- report suspected adverse drug reactions to fluoroquinolone antibiotics on the [Yellow Card website](#) or via the Yellow Card app (download it from the [Apple App Store](#), or [Google Play Store](#))

Advice for healthcare professionals to provide to patients:

- fluoroquinolones are a class of antibiotics that include ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, and ofloxacin – these medicines may also have a brand name so patients should check the details of all antibiotics prescribed to them
- fluoroquinolone antibiotics have been reported to cause serious side effects involving tendons, muscles, joints, nerves, or mental health – in some patients, these side effects have caused long-lasting or permanent disability
- stop taking your fluoroquinolone antibiotic and contact your doctor immediately if you have any of the following signs of a side effect:
 - tendon pain or swelling – if this happens, rest the painful area until you can see your doctor
 - pain in your joints or swelling in joints such as in the shoulders, arms, or legs
 - abnormal pain or sensations (such as persistent pins and needles, tingling, tickling, numbness, or burning), weakness in the legs or arms, or difficulty walking
 - severe tiredness, depressed mood, anxiety, problems with your memory or severe problems sleeping
 - changes in your vision, taste, smell or hearing

Tell your doctor if you have had any of the above effects at any point while taking a fluoroquinolone – this means you should avoid them in the future

Side effects of systemic fluoroquinolones

Systemic and inhaled fluoroquinolones are associated with a risk of serious, disabling, long-lasting and potentially irreversible adverse reactions, estimated to occur in at least between 1 and 10 people in every 10,000 who take a fluoroquinolone. These may affect multiple body systems and include musculoskeletal, nervous, psychiatric and sensory reactions. These adverse reactions have been reported in patients irrespective of their age and potential risk factors.

Patients have reported that experiencing long-lasting or disabling reactions can affect their mental health, particularly when they perceive healthcare professionals fail to adequately acknowledge the reactions or the possibility that they are associated with a fluoroquinolone. Tendon damage can occur within 48 hours of commencing treatment, or the effects can be delayed for several months and become apparent after stopping treatment.

There are no proven drug treatments for these side effects. However, it is important that fluoroquinolones are stopped immediately at the first signs of a musculoskeletal, neurological or psychiatric side effect, such as those described above to avoid further

exposure, which could potentially worsen adverse reactions. These symptoms should be appropriately investigated.

MHRA review and further limits to the use of fluoroquinolones

[Restrictions to the use of fluoroquinolones](#) were introduced in 2019 to minimise the risk of these reactions. The MHRA has reviewed the effectiveness of these measures in the UK and sought the advice of the Commission on Human Medicines (CHM). As a result of this review a reminder about these risks was published in the [August 2023 issue of Drug Safety Update](#).

The MHRA has now taken additional regulatory action to update the indications for all systemic fluoroquinolones to state they should only be used when other commonly recommended antibiotics are inappropriate. Situations where other antibiotics are considered to be inappropriate are where:

- there is resistance to other first-line antibiotics recommended for the infection
- other first-line antibiotics are contraindicated in an individual patient
- other first-line antibiotics have caused side effects in the patient requiring treatment to be stopped
- treatment with other first-line antibiotics has failed

The description of disabling and potentially long-lasting or irreversible side effects in the safety information has also been updated, to include more detail about the range of psychiatric symptoms that may occur as part of these reactions. These may include sleep disorders, anxiety, panic attacks, confusion or depression. While the frequency of disabling and potentially long-lasting or irreversible side effects cannot be estimated precisely using available data, the updated reporting incidence indicates a minimum frequency of between 1 and 10 per 10,000 patients.

Report any suspected adverse drug reactions

Please continue to report suspected adverse drug reactions to fluoroquinolones 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, SystmOne, 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.

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Omega-3-acid ethyl ester medicines (Omacor/Teromeg 1000mg capsules): dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors

Systematic reviews and meta-analyses of randomised controlled trials have highlighted a dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl ester medicines compared to placebo.

Advice for healthcare professionals:

- atrial fibrillation is now listed as an adverse drug reaction with a “common” frequency (may affect up to 1 in 10 people) for medicines containing omega-3-acid ethyl esters licensed for the treatment of hypertriglyceridaemia
- the observed risk was found to be highest with a dose of 4 g/day
- advise patients taking omega-3-acid ethyl ester medicines for the treatment of hypertriglyceridaemia to seek medical attention if they develop symptoms of atrial fibrillation
- if a patient develops atrial fibrillation whilst taking these medicines for the treatment of hypertriglyceridaemia then the medicine should be discontinued permanently
- report suspected adverse drug reactions associated with omega-3-acid ethyl ester medicines on a [Yellow Card](#)

Advice for healthcare professionals to provide to patients:

- medicinal products containing omega-3 ethyl esters are licensed for the reduction of high triglyceride levels (hypertriglyceridaemia) after changes to diet have not worked
- very high levels of triglycerides in the blood can cause problems such as increasing the risk of coronary heart disease and causing inflammation of the pancreas (pancreatitis)
- before taking an omega-3-acid ethyl ester medicine, inform your doctor or pharmacist if you are currently experiencing heart problems or have a history of heart problems
- talk to your doctor if you experience palpitations, dizziness, shortness of breath and tiredness as these may be symptoms of an irregular and often very rapid heart rhythm (atrial fibrillation)
- do not stop your hypertriglyceridaemia treatment without first discussing this with your doctor

Review of atrial fibrillation associated with omega-3-acid ethyl ester medicines

A recent European regulatory [review](#) recommended “atrial fibrillation” should be listed as a common adverse reaction (may affect up to 1 in 10 people) in the product information of medicines containing omega-3-acid ethyl esters. The review of safety and efficacy data for omega-3 acid ethyl ester medicines licensed for the treatment of

hypertriglyceridaemia considered a dose-dependent increased risk of atrial fibrillation which had been identified by several meta-analyses of large randomised controlled trials (RCTs). These trials investigated the effect on cardiovascular outcomes compared with placebo enrolling more than 80,000 patients, mostly with cardiovascular diseases or cardiovascular risk factors.^{1,2,3} The frequency of atrial fibrillation was determined as "common" since, from this data, the incidence would be 3.9%.

The findings of this review were considered by the Pharmacovigilance Expert Advisory Committee (PEAG) of the [Commission on Human Medicines](#) (CHM), which agreed with the recommendations of European regulators to update the product information. A letter has been sent to UK healthcare professionals. The PEAG also recommended issuing a Drug Safety Update to inform healthcare professionals and patients about the new information.

The product information recommends permanent discontinuation of treatment for patients who develop atrial fibrillation whilst taking these medicines for hypertriglyceridaemia. Clinical judgment and assessment of the individual benefits and risks to the patient should be taken into consideration before any decision to stop treatment.

The PEAG noted that, in the case of patients with a previous or current diagnosis of atrial fibrillation, the Product Information does not provide specific advice or contraindicate use of these medicines.

Omega-3 dietary sources and supplements

The MHRA does not regulate food or dietary supplements that are marketed without reference to a medicinal effect/claim. Neither the randomised controlled trials or the review evaluated dietary consumption of fish and other foods rich in omega-3 nor supplements, and we are unable to give advice on the risk in individuals who consume dietary omega-3 supplements without a known history of cardiovascular disease or significant cardiovascular risk factors.

Reports of atrial fibrillation with omega-3-containing products

Up to 13 November 2023, the MHRA has not received any Yellow Card reports describing atrial fibrillation in association with a medicinal product containing omega-3 acids as the active substance.

Atrial fibrillation is an abnormal heart rhythm characterised by a fast irregularly irregular heart rate. Symptoms of atrial fibrillation include palpitations, dizziness, shortness of breath and tiredness. If untreated it can cause formation of blood clots in the heart which may travel to the brain (embolise), leading to a stroke.

Other omega 3 ethyl ester medicines

Vazkepa (icosapent ethyl) authorised in 2021 is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L]) and established cardiovascular disease, or diabetes, and at least one other cardiovascular risk factor. Icosapent ethyl

is a stable ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid (EPA). At time of initial authorisation of this medicinal product, atrial fibrillation/flutter was listed as a common adverse drug reaction. The incidence of atrial fibrillation/flutter was 5.8% of subjects receiving icosapent ethyl in a placebo-controlled cardiovascular outcomes trial compared with 4.5% in subjects receiving placebo.

Several parenteral infusion products that contain omega 3 acid triglycerides or omega-3 fish oil are licensed as prescription only medicines in the UK. These products do not currently list atrial fibrillation as a recognised adverse drug reaction. At this time they are not directly impacted by the regulatory action that has been taken.

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, SystmOne, 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.

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Letters and medicine recalls sent to healthcare professionals in December 2023

A summary of recent letters and notifications sent to healthcare professionals about medicines and medical devices.

Letters

In December 2023, the following letters were sent or provided to relevant healthcare professionals:

- [Oncaspar 750 U/ml powder for solution for injection/infusion: Interim Supply of Irish Stock to Mitigate Supply Disruption](#)
- [Biktarvy 30 mg/120 mg/15 mg film-coated tablets \(bictegravir 30mg/ emtricitabine 120mg/ tenofovir alafenamide 15mg\): Interim Supply of Ireland-Northern Ireland-Malta Stock to Mitigate Supply Disruption](#)
- [Xevudy® \(sotrovimab\) 500 mg concentrate for solution for infusion: Important information for healthcare professionals about the expiry date of all packs](#)
- [VERORAB, powder and solvent for suspension for injection: Interim Supply of UK Stock in Standard Export Packaging \(Standard Export Packs\) to Mitigate Supply Disruption](#)

Medicine Recalls and Notifications

In December 2023, recalls and notifications for medicines were issued on:

[Class 4 Medicines Defect Information: Strandhaven Ltd t/a Somex Pharma, Tramadol Hydrochloride 50mg Capsules, Hard, EL \(23\)A/41](#). Issued on 6 December 2023.

Strandhaven Limited t/a Somex Pharma has informed the MHRA regarding an error with the Patient Information Leaflets (PILs) that have been packed in the listed batches of Tramadol Hydrochloride 50mg Capsules, Hard. The PIL does not include the most up to date safety information for drug interaction of antidepressants with Tramadol, sleep-related breathing disorders, adrenal insufficiency, hiccups, and serotonin syndrome, and the need to seek medical advice if they occur.

[Class 4 Medicines Defect Information: Strandhaven Ltd t/a Somex Pharma, Clarithromycin 250mg and 500mg film-coated tablets, EL \(23\)A/42](#). Issued 6 December 2023. Strandhaven Limited t/a Somex Pharma has informed the MHRA regarding an error with the Patient Information Leaflets (PILs) that have been packed in the listed batches of Clarithromycin 250mg and 500mg film-coated tablets. The PIL does not include the most up to date safety information.

[Class 4 Medicines Defect Information: Atnahs Pharma UK Limited, Clobazam Atnahs 5mg/5ml and 10mg/5ml Oral Suspension, EL\(23\)A/43](#). Issued 13 December 2023. Atnahs Pharma UK Ltd has informed the MHRA that the batches of Clobazam Atnahs 5mg/5ml and 10mg/5ml Oral Suspension listed in this notification do not contain the most up to date safety information. The Summary of Product Characteristics (SmPC) and the Patient Information Leaflets (PIL) present in the pack are missing significant information. This is in relation to the use of the product in children (contraindicated), pregnancy, depression,

drug dependence, numerous interactions and adverse effects which are missing from the PIL present in the pack and in the SmPC.

[Class 3 Medicines Recall: Biocon Pharma UK Ltd., Posaconazole Biocon 100mg Gastro-resistant Tablets, EL\(23\)A/44](#). Issued 14 December 2023. Biocon Pharma UK Limited are recalling a specific of batch Posaconazole 100mg Gastro-resistant Tablets due to an out of trend result for unspecified impurities during testing for stability. The batch is likely to be out of specification before the expiry date and therefore the batch is being recalled as precautionary measure.

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