



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>

First, we inform healthcare professionals of a very small number of reports of new-onset or aggravation of pre-existing myasthenia gravis associated with statin medicines. We ask prescribers to advise patients taking statins to be alert to the onset of new symptoms for myasthenia gravis, or worsening symptoms of pre-existing myasthenia gravis, and to seek medical advice if these occur.

Our second article reminds healthcare professionals prescribing fluoroquinolone antibiotics (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin) to be alert to the risk of psychiatric reactions, including depression or psychotic reactions, which may potentially lead to thoughts of suicide or suicide attempts.

Our final article provides a summary of recent letters and notifications sent to healthcare professionals about medicines. If you have been forwarded this issue of Drug Safety Update, [subscribe directly via our website](#).

Statins: very infrequent reports of myasthenia gravis

Globally, there has been a very small number of reports of new-onset or aggravation of pre-existing myasthenia gravis with atorvastatin, pravastatin, lovastatin, fluvastatin, simvastatin, rosuvastatin and pitavastatin (single-ingredient and fixed-dose combination products). Advise patients taking statins to be alert to new symptoms for myasthenia gravis, or worsening symptoms of pre-existing myasthenia gravis, and to seek medical advice if these occur.

Advice for healthcare professionals:

- there have been some suspected reports of new-onset or aggravation of pre-existing myasthenia gravis or ocular myasthenia associated with statin use; the current frequency of these adverse events is not known but given the extensive use of statins in the population, the reports are understood to be very infrequent
- the majority of UK reports note that the patient recovered after stopping statin treatment, while a minority continued to experience symptoms; recurrence of symptoms has been reported when patients restarted on the same or a different statin
- refer patients presenting with suspected new-onset myasthenia gravis after starting statin therapy to a neurology specialist – it could be necessary to discontinue statin treatment depending on the assessment of the individual benefits and risks
- advise patients with pre-existing myasthenia gravis to be alert to aggravation of symptoms while taking a statin (see advice below); it could be necessary to discontinue statin treatment depending on the assessment of the individual benefits and risks
- report suspected adverse drug reactions associated with statins on a [Yellow Card](#)

Advice for healthcare professionals to provide to patients, parents and carers:

- statins are important medicines to lower a person's risk of having cardiovascular events such as angina, heart attacks and stroke
- many people who take statins do not experience side effects and, where this does happen, these are typically mild – but it is important to read the Patient Information Leaflet that comes with your medicine and talk to a healthcare professional if you are experiencing problems
- do not stop your statin treatment without first discussing this with your doctor
- before taking a statin, inform your doctor if you have history of myasthenia gravis or ocular myasthenia
- talk to your doctor if you experience weakness in your arms or legs that worsens after periods of activity, double vision or drooping of your eyelids, difficulty swallowing, or shortness of breath
- seek medical help immediately if you develop severe breathing or swallowing problems

Review of myasthenia gravis associated with statin medicines

Statins are an acceptably safe and effective group of medicines that help lower the level of low-density lipoprotein (LDL) cholesterol in the blood. Statins play an important role in the treatment of atherosclerotic cardiovascular disease (narrowing and hardening of arteries). Currently available statins in the UK are atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.

A [recent European review recommended new warnings](#) on the risk of new onset or aggravation of pre-existing myasthenia gravis with multiple statins.¹ 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.

In reviewing this issue, the PEAG recommended that the MHRA inform healthcare professionals and patients of the newly identified risk. They also noted that existing [International Consensus Guidance for Management of Myasthenia Gravis](#) (2020) states that statins may rarely worsen or precipitate myasthenia gravis.²

About myasthenia gravis

Myasthenia gravis is a rare long-term auto-immune neuromuscular disorder characterised by fluctuating weakness of the voluntary muscles that control eye movements, facial expression, speaking, swallowing, limb movement and breathing. Symptoms include drooping eyelids, double vision, problems with chewing or swallowing, speech disturbance, limb weakness and shortness of breath.

Myasthenia gravis can affect people of any age, generally starting in women under 40 years old and men over 60 years old. Drug treatment can usually help keep the symptoms under control. Several triggers have been identified for patients with myasthenia gravis that can aggravate symptoms. These include stress, tiredness, infections, excess physical activity, surgery, changes in immunomodulatory treatments, and medicines. Some examples of medicines that have been associated with worsening symptoms include several groups of antibiotics (fluoroquinolones, macrolides, aminoglycosides) and beta-blockers. Reports of worsening myasthenia gravis with medicines are very rare.

UK reports of myasthenia gravis with statins

From 14 June 1995 up to 19 June 2023, the MHRA has received 10 UK Yellow Card reports citing a statin as a suspect medicine for an adverse drug reaction (ADR) involving myasthenia gravis; with reports received for simvastatin, atorvastatin and pravastatin. This is against a background of extensive use of statins. In 2022 alone, more than 9.5 million patients were dispensed a statin in the UK.³

Across the 10 Yellow Card reports the median age of the patients was 66 years (affected patient age groups ranged from 40 to 89 years with the majority of reports

concerning those aged over 60 years). Symptoms reported include double vision, difficulty with speech and swallowing, weakness in limbs and shortness of breath. Onset of symptoms started from a few days up to three months after starting statin therapy.

Three of the 10 cases involved the recurrence or exacerbation of symptoms in patients with known myasthenia gravis. There was also one report of positive rechallenge with symptoms recurring on reinitiating statin therapy. While four of the reports indicated that patients were hospitalised, the majority of patients had recovered or were recovering at the time of reporting. No fatal UK reports have been received.

At this time there is insufficient data to conclude whether different statins, different duration of therapy and different dosing levels alter the risk of experiencing myasthenia gravis. It is also unknown whether the development of new-onset myasthenia gravis following statin therapy is a transient or permanent condition.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to 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.

References

1. [PRAC recommendations on signals: Adopted at the 9-12 January 2023 PRAC meeting \(EMA/PRAC/4770/2023\)](#). ↵
2. Narayanaswami P and others. [International Consensus Guidance for Management of MG - 2020 Update. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update](#). Neurology 2021; issue 96 pages 114 to 122.
3. Estimated number of UK patients dispensed a statin. The UK estimate was derived from dispensing data for England. The dispensing data was extracted from NHS Business Services Authority (NHSBSA) ePACT2 by MHRA in August 2023.

Article citation: Drug Safety Update volume 17, issue 2: September 2023: 1.

Fluoroquinolone antibiotics: suicidal thoughts and behaviour

Healthcare professionals prescribing fluoroquinolone antibiotics (ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, ofloxacin) are reminded to be alert to the risk of psychiatric reactions, including depression and psychotic reactions, which may potentially lead to thoughts of suicide or suicide attempts. Healthcare professionals are also reminded to advise patients to be alert to these risks.

Advice for healthcare professionals:

- advise patients to carefully read the advice in the Patient Information Leaflet about possible psychiatric reactions, and to seek medical advice if they experience these symptoms
- when prescribing a fluoroquinolone, advise patients to be alert to any mood changes, distressing thoughts, or feelings about suicide or harming themselves at any point during treatment
- note that fluoroquinolones can exacerbate existing psychiatric symptoms
- advise patients to seek medical advice if they develop such thoughts or behaviours, and ensure that a suitable referral for treatment is made, if necessary
- fluoroquinolones should be discontinued at the first signs of a serious adverse reaction, including new or worsening depression or psychosis
- report suspected adverse drug reactions (ADRs) to the [Yellow Card scheme](#)

Advice for healthcare professionals to provide to patients and caregivers:

- fluoroquinolone antibiotics are a group of antibiotics that include ciprofloxacin, delafloxacin, levofloxacin, moxifloxacin, and ofloxacin – sometimes these medicines may also have a brand name so patients should check the details of all antibiotics prescribed to them
- if you are prescribed one of the antibiotics listed above and you suffer from depression or psychosis, tell your healthcare professional – this is important as your symptoms may become worse under treatment
- psychiatric reactions include confusion, disorientation, anxiety, depression and suicidal thoughts or suicide attempts
- you may not notice some changes in your mood and behaviour so it is very important to tell your friends and family that you are taking these medicines, and that they have rare psychiatric side effects associated with them – others may notice changes and help you quickly identify any symptoms that you need to talk to your doctor about
- if you develop thoughts of suicide or have attempted suicide, do not take any further doses of your fluoroquinolone, and talk to your doctor or another healthcare professional immediately

Reports of suicidal ideation and behaviour

The MHRA has received a Coroner's report following the death of a patient who died by suicide after being treated with ciprofloxacin. The patient had no previous history of depression or mental health problems. The Coroner raised concerns about the potential risk of suicidal behaviour in patients taking ciprofloxacin, the potential for increased risk in patients with depression, and the need to highlight this to healthcare professionals.

Warnings on the potential for psychiatric adverse drug reactions to occur with ciprofloxacin and other fluoroquinolones are included in the product information. The [Summary of Product Characteristics](#) (SmPC) states that psychiatric reactions may occur with ciprofloxacin, including after the first dose. In rare cases, depression or psychosis can progress to suicidal ideation or suicide attempts. If this happens, ciprofloxacin should be discontinued immediately.

The [Patient Information Leaflet](#) (PIL) advises patients that they may experience psychiatric reactions. If patients suffer from depression or psychosis before being prescribed this medication, their symptoms may become worse under treatment with ciprofloxacin. In rare cases, depression or psychosis can progress to thoughts of suicide or suicide attempts. If this happens, patients are advised to contact their doctor immediately.

It is not possible from available data to indicate a frequency nor period of risk for these potential adverse reactions. Patients should be advised to seek medical attention for any psychiatric symptoms, even if it has been some time since they stopped taking the medication.

Report any suspected adverse drug reactions

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.

Article citation: Drug Safety Update volume 17, issue 2: September 2023: 2.

Letters and medicine recalls sent to healthcare professionals in August 2023

A summary of recent letters and notifications sent to healthcare professionals about medicines, and a recent national patient safety alert highlighting the risk of deaths and serious injuries from entrapment or falls relating to medical beds, bed rails, trolleys, bariatric beds, lateral turning devices and bed grab handles.

National Patient Safety Alert: Medical beds, trolleys, bed rails, bed grab handles and lateral turning devices: risk of death from entrapment or falls (NatPSA/2023/010/MHRA)

On 30 August, we issued a [National Patient Safety Alert](#) to support organisations to update their policies and procedures on procurement, provision, prescribing, servicing and maintenance of these devices in line with the MHRA's updated [guidance on the management and safe use of bed rails](#). This follows reports of deaths and serious injuries from entrapment or falls relating to medical beds, bed rails, (also known as bed safety rails), trolleys, bariatric beds, lateral turning devices and bed grab handles (also known as bed levers or bed sticks).

Letters

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

- [Cisplatin 1 mg/ml Sterile Concentrate - Temporary supply of unlicensed imported product](#)
- [ONIVYDE pegylated liposomal 4.3 mg/ml concentrate for dispersion for infusion. Interim Supply of Irish packs \(common pack for Republic of Ireland and Northern Ireland\) to Mitigate Supply Disruption](#)
- [Ozempic ▼ \(semaglutide\), Rybelsus ▼ \(semaglutide\) and Victoza \(liraglutide\): GLP-1 Receptor Agonists Supply Shortage in the UK](#)
- [Simponi \(golimumab\) 50 mg and 100 mg: Important changes to the injection instructions for the SmartJect Pre-filled Pen](#)
- [Xalkori \(crizotinib\): Vision disorders, including risk of severe visual loss, need for monitoring in paediatric patients](#)
- [Dailiport \(tacrolimus\) 3 mg prolonged-release hard capsules Temporary supply of Dailiport 3mg in Belgian packaging](#)
- [Replacement BAXJECT II / BAXJECT II Hi-Flow Reconstitution Devices co-packaged with ADVATE or FEIBA](#)

Medicine Recalls and Notifications

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

[Class 2 Medicines Recall: medac GmbH \(t/a medac Pharma LLP\), Sodiofolin 50 mg/ml solution for injection/infusion, \(100mg/2ml vial\), EL \(23\)A/28](#). Issued 21 August 2023.

Further to EL(23)/A26 medac GmbH (t/a medac Pharma LLP) has informed the MHRA that further batches that are impacted have been identified. medac GmbH (t/a medac Pharma LLP) is recalling the products and respective batches in the notification due to particles detected during long-term stability tests. Healthcare professionals are advised to stop supplying the batched referred to in the recall. Quarantine all remaining stock and return it to your supplier using your supplier's approved process.

[Class 4 Medicines Notification, Accord Healthcare Limited, UK, Olmesartan Medoxomil 10mg film coated tablets, EL \(23\)A/29](#). Issued 22 August 2023. Accord Healthcare Ltd, UK has informed the MHRA about an error with the Patient Information Leaflets (PILs) that have been packaged in the batches referred to in the notification. The PIL does not include the most up-to-date safety information regarding the signs and symptoms of liver issues and the need to seek medical advice if they occur. There is no risk to product quality as a result of this issue, therefore the affected batches are not being recalled. Healthcare professionals are advised to exercise caution when dispensing the product and where possible, provide an updated PIL, which can be downloaded from the [Accord website](#).

[Class 4 Medicines Notification, Accord Healthcare Limited, UK, Irinotecan Hydrochloride 20 mg/ml Concentrate for Solution for Infusion, EL \(23\)A/30](#). Issued 23 August 2023. Accord Healthcare Ltd, UK has informed the MHRA about an error with the Patient Information Leaflets (PILs) that have been packaged in the batches referred to in the notification. The PIL does not include the most up-to-date safety information regarding the contraindication for Gilbert's syndrome. There is no risk to product quality as a result of this issue, therefore the affected batches are not being recalled. Healthcare professionals are advised to exercise caution when dispensing the product and where possible, provide an updated PIL, which can be downloaded from the [Accord website](#).

[Class 4 Medicines Defect Information: Galderma \(U.K.\) Limited, Loceryl 5% w/v Medicated Nail Lacquer \(5.0 ml\), EL \(23\)A/31](#). Issued 29 August 2023. Galderma (U.K.) Limited has informed the MHRA that a pallet of Loceryl 5% w/v Medicated Nail Lacquer from a batch licensed only for distribution in Ireland has been inadvertently placed into the UK supply chain due to a warehousing error at their UK pre-wholesaler. Although Loceryl is a registered medicine in both Ireland and the UK, there are differences between these products in the product labelling and Patient Information Leaflet (PIL) packaged with the medicine. The details of the key packaging differences for Ireland versus the UK product have been risk-assessed as having minimal safety implications for the patient. Healthcare professionals are advised to exercise caution when dispensing the affected batch of Loceryl 5% w/v Medicated Nail Lacquer. Where possible, please provide the current [UK-](#)

[approved copy of the PIL](#) to the patient and remind them to read the leaflet in its entirety before using the medicine.

[Class 2 Medicines Recall: Veriton Pharma Limited, Epistatus 2.5 mg oromucosal solution, pre-filled syringe \(PFS\), EL\(23\)A/32](#). Issued 30 August 2023. Veriton Pharma Limited is recalling a specific batch of Epistatus (midazolam) 2.5mg Oromucosal Solution (pre-filled oral syringes) due to confirmed out of specification results related to the product appearance. The recall is being carried out as a precautionary measure. Stop supplying the affected batch immediately. Quarantine all remaining stock and return it to your supplier using your supplier's approved process. Healthcare settings should consider using other batches or midazolam from alternative providers to administer emergency doses as required. The opalescent product in the impacted batch has been shown to contain sufficient midazolam and could be used in an emergency where alternate medicine is not available.

[Class 4 Medicines Defect Information: Kyowa Kirin Limited, Tostran \(Testosterone, 2% gel\), EL \(23\)A/33](#). Issued 31 August 2023. Kyowa Kirin Limited has notified the MHRA that the priming instructions in the current PIL for Tostran 2% gel require updating. Following a manufacturing change to the Tostran 2% gel dosage pump/dispenser system, the manufacturer has observed that the priming instruction requires changing. The number of actuations required to prime the device to achieve correct dosing increases over time. This means that more pumps are now required to prime the device before using it for the first time. If these instructions are not followed then a less accurate first dose may be delivered. Healthcare professionals are advised to inform patients that there was a change to the pump/dispenser device supplied with this medicine and the priming instructions prior to use in the current PIL are not accurate.

Article citation: Drug Safety Update volume 17, issue 12: September 2023: 3.