Drug Safety Update

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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Contents

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.

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In this edition of Drug Safety Update we have new warnings about the use of denosumab 60mg (Prolia) in children and adolescents younger than 18 years. These warnings follow serious and life-threatening cases of hypercalcaemia in paediatric clinical trials and during off-label use. Denosumab 60mg is authorised only in adults with osteoporotic conditions – it should not be used in children and adolescents younger than 18 years. Denosumab 120mg (as Xgeva) remains authorised for skeletally mature adolescents with giant cell tumour of bone (in addition to other indications).

On page 5, we summarise recent advice relating to COVID-19 vaccines and medicines published since the April 2022 issue of Drug Safety Update.

And on page 6, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines and medical devices. This includes a recall of Accupro (quinapril hydrochloride) and recent advice on Xagrid (anagrelide hydrochloride).

Denosumab 60mg (Prolia): should not be used in patients under 18 years due to the risk of serious hypercalcaemia

Serious and life-threatening hypercalcaemia has been reported with denosumab 60mg (Prolia) in children and adolescents in clinical trials for osteogenesis imperfecta and during off-label use. Denosumab 60mg (Prolia) is authorised for use in adults with osteoporosis and other bone loss conditions – it should not be used in children and adolescents younger than 18 years.

Advice for healthcare professionals:

- denosumab 60mg (Prolia) is authorised for use only in adults (aged 18 years and older) for treatment of osteoporosis and other bone loss conditions
- serious and life-threatening hypercalcaemia has been reported with denosumab 60mg use in children and adolescents in clinical trials and during off-label use
- hypercalcaemia cases occurred during treatment or in the weeks to months after the last dose
- denosumab 60mg (Prolia) should not be used in children and adolescents younger than 18 years
- denosumab 120mg (as Xgeva) remains authorised for skeletally mature adolescents with giant cell tumour of bone (alongside other authorisations – see Denosumab section on page 3)
- report any suspected adverse drug reactions associated with denosumab or other medicines on a Yellow Card

Advice for healthcare professionals to give to patients or parents and caregivers:

- denosumab 60mg (known as Prolia) is a medicine in adults to treat osteoporosis and other conditions associated with thinning of the bones and an increased risk of fractures
- there have been serious cases of hypercalcaemia (increased calcium in the blood) in children and teenagers receiving denosumab treatment outside of the currently approved indications
- patients on Prolia who are younger than 18 years, and their parents or caregivers, should talk to their specialist about what this means for them
- denosumab 120mg (known as Xgeva) remains authorised for skeletally mature teenagers with some bone tumours (alongside other authorisations – see Denosumab section on page 3)
- all patients on denosumab should read carefully the Patient Information Leaflet and Patient Reminder Card and speak to a healthcare professional if they are concerned about side effects

Denosumab and effects on calcium levels

Denosumab 60mg (Prolia) is indicated in adults for the treatment of osteoporosis in postmenopausal women and men at increased risk of fractures. It is also indicated in adults for treatment of bone loss associated with long-term systemic glucocorticoid therapy or hormone ablation in prostate cancer, in patients who are at increased risk of fractures.

Denosumab 120mg (Xgeva) is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity. Denosumab 120mg is also indicated in adults for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) with advanced malignancies involving bone.

Denosumab is a monoclonal antibody (IgG2) that prevents bone loss by blocking RANK receptor on the surface of osteoclast precursors and osteoclasts, therefore decreasing bone breakdown. By doing this, bones become stronger and less likely to break easily.

By making bones stronger, denosumab has been associated with low levels of calcium in the blood (hypocalcaemia) – see Drug Safety Update articles from October 2012 and September 2014).

Denosumab 120mg has also been associated with high levels of calcium in the blood (hypercalcaemia) after stopping treatment (rebound hypercalcaemia) in patients with giant cell tumour of bone – see section below.

Cases of hypercalcaemia in children and adolescents with denosumab 60mg

Cases of serious and life-threatening hypercalcaemia requiring hospitalisation and complicated by acute renal injury have been reported in children and adolescents younger than 18 years receiving 60mg denosumab in clinical trials.

These clinical trials were investigating treatment with denosumab in patients younger than 18 years with osteogenesis imperfecta. Osteogenesis imperfecta is a group of rare inherited conditions that cause very fragile bones.

Worldwide, we are also aware of 20 suspected adverse event reports of hypercalcaemia reported up to 26 August 2021, during off-label treatment with Prolia in children and adolescents younger than 18 years. Reports included cases in paediatric patients with osteogenesis imperfecta, as well as in those with various other conditions. There were also a small number of reports of hypercalcaemia in patients younger than 18 years after stopping treatment (rebound hypercalcaemia).

Symptoms of hypercalcaemia include excessive thirst, excessive urination, drowsiness, confusion, loss of concentration, feeling or being sick, constipation, and muscle weakness. Severe hypercalcaemia can cause serious kidney problems (acute renal injury), coma, heart rhythm abnormalities and cardiac arrest.

Review and updates to advice

A recent European review assessed these cases of severe hypercalcaemia and recommended stronger warnings against use of Prolia in children and adolescents younger than 18 years. We have considered this review together with the safety data and agree that the product information should be updated.

The Summary of Product Characteristics (SmPC) for Prolia will advise that denosumab 60mg should not be used in children and adolescents younger than 18 years because of safety concerns about serious hypercalcaemia. There are also existing warnings that inhibition of RANK/RANK ligand (RANKL) in animal studies may be associated with inhibition of bone growth and lack of tooth eruption.

Denosumab 120mg and risks of clinically significant hypercalcaemia

The SmPC for Xgeva advises that clinically significant hypercalcaemia is a known risk after stopping denosumab 120mg in patients with growing skeletons. Due to the risks, denosumab 120mg is not recommended in patients with growing skeletons.

Clinically significant hypercalcaemia has also been reported in skeletally-mature adolescents and adults for giant cell tumour of bone, sometimes occurring weeks to months after treatment discontinuation (rebound hypercalcaemia) – see advice in Drug Safety Update Xgeva and risk of rebound hypercalcemia.

Report suspected reactions on a Yellow Card

Please continue to report any 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.

Report suspected side effects to medicines, vaccines or medical device and diagnostic adverse incidents used in coronavirus (COVID-19) 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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COVID-19 vaccines and medicines: updates for May 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the April 2022 issue of Drug Safety Update, up to 13 May 2022.

Removal of 15-minute observation period following vaccination with COVID-19 Vaccine Pfizer/BioNTech or Moderna

The 15-minute observation period following vaccination with COVID-19 Vaccine Pfizer/BioNTech or Moderna has been removed for individuals aged 12 years and over who have no history of a severe allergic reaction (as outlined in the Green Book advice).

This follows careful review of the safety data by us and advice from the government's independent Commission on Human Medicines. A temporary suspension of the 15-minute observation period for children aged 5-11 years remains in place and this will be reviewed on a regular basis.

Summaries of Yellow Card reporting and other recent MHRA publications

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.

We have also recently:

- published the Public Assessment Report for Nuvaxovid COVID-19 vaccine. Please see the Decision page on our website which has more details about the Nuvaxovid COVID-19 vaccine.
- updated the Summary of Product Characteristics and Patient Information Leaflet of COVID-19 Vaccine Janssen to include transverse myelitis as a possible side effect

We previously included summaries of latest COVID-19 information, including in the February 2022, March 2022 and April 2022 issues of Drug Safety Update. See guidance on COVID-19 for all our latest information, including after publication of this article.

Reporting Yellow Cards

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 via the Yellow Card app.

As these products are under additional monitoring, this includes all suspected adverse reactions associated with these vaccines. This will allow quick identification of new safety information. When reporting please provide as much information as possible, including information about medical history, any concomitant medications, onset, treatment dates, and vaccine product brand name and batch number.

You may be contacted following submission of a Yellow Card report so that we can gather additional relevant information for the assessment of the report. These contributions form an important part of our understanding of suspected adverse events.

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Letters and medicine recalls sent to healthcare professionals in April 2022

Recall of Accupro (quinapril hydrochloride)

On 5 May 2022, all Accupro (quinapril hydrochloride) tablets were recalled at pharmacy and wholesale level as a precautionary measure due to the observation of levels of N-nitroso-quinapril (an impurity) above the acceptable daily intake level.

As a result of the recall, Accupro will not be available to dispense from pharmacies. Currently no information can be provided for when Accupro will be available again.

Based on the available data, there is no immediate risk to patients who have been taking this medication. Advise patients undergoing treatment not to discontinue Accupro without consulting with their prescriber, as there are potential risks associated with suddenly stopping treatment for blood pressure.

See accompanying letter to provide advice to prescribers on impact on patient treatment. For patients who are already taking Accupro, it will not be possible to continue treatment and the prescribing healthcare professionals should review their hypertension treatment and switch patients to a suitable alternative.

Xagrid (anagrelide hydrochloride): Risk of thrombosis if treatment discontinued abruptly

Anagrelide hydrochloride is indicated for the reduction of elevated platelet counts in at-risk patients with essential thrombocythaemia who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. Following a European review, new warnings were introduced to avoid abrupt discontinuation and a letter sent to prescribers.

There is an increased risk of thrombotic complications, including cerebral infarction, if anagrelide treatment is discontinued abruptly. In the event of dosage interruption or treatment withdrawal, monitor platelet counts frequently.

Other Letters

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

- Kevzara▼ 200 mg solution for injection in pre-filled pen (sarilumab): interim supply of German stock to mitigate supply disruption
- Stamaril, powder and solvent for suspension for injection in pre-filled syringe – yellow fever vaccine (live): interim supply of EU stock in standard export packaging (standard export packs) to mitigate supply disruption

Other Medicine Recalls and Notifications

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

Class 2 Medicines Recall: USV UK Limited, Olopatadine USV 1mg/ml Eye Drops, Solution, EL(22)A/17. Issued 11 April 2022. Batches of Olopatadine (olopatadine hydrochloride) USV 1mg/mL eye drops are being recalled due to out of specification results for impurities during stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 4 Medicines Defect Information: Pfizer Limited, Depo-Medrone with Lidocaine 40 mg/mL (1 mL and 2 mL vials – single vial preparations), EL (22)A/18. Issued 21 April 2022. Batches of Depo-Medrone with Lidocaine (Methylprednisolone acetate and Lidocaine hydrochloride) 40 mg/mL have been identified to contain an out-dated Patient Information Leaflet. The leaflets omits information including warning and precautions and risk of low birth weight of the baby if used in pregnancy, and the leaflet contains out of date adverse reaction frequencies. Healthcare professionals administering medicine from the affected batches are asked to provide the correct Patient Information Leaflet, to ensure that appropriate patient counselling takes place and patients are aware of the missing information.

Class 2 Medicines Recall: Crescent Pharma Limited, Paroxetine 40mg Film Coated Tablets, EL(22)A/19. Issued 27 April 2022. A batch of paroxetine 40mg film coated tablets is being recalled due to out of specification results for dissolution during routine stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 2 Medicines Recall: Fresenius Kabi Limited, Sodium bicarbonate 1.26% Solution for infusion, EL(22)A/20. Issued 28 April 2022. A batch of Sodium bicarbonate 1.26% Solution for infusion is being recalled as a precautionary measure due to identification of particles in the solution for infusion. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Medical Device Safety Information

In April 2022, MHRA Device Safety Information pages have been published on:

Paclitaxel drug-coated balloons (DCBs) or drug-eluting stents (DESs): Updated position on use in patients with critical limb ischaemia and intermittent claudication DSI/2022/003. Issued 5 April 2022. In 2021 the MHRA convened an independent Expert Advisory Group to review new evidence for paclitaxel drug-coated balloons and paclitaxel drug eluting stents. The MHRA's recommendations for using paclitaxel-coated devices in patients with intermittent claudication and critical limb ischaemia have been updated to take into account potential dose dependent effects of paclitaxel coated balloons and stents in patients. Actions for clinicians are available in the device safety information.

For all of the latest safety notices from the MHRA on drugs and medical devices, see Alerts and recalls for drugs and medical devices.

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