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** is the government agency which is 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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New recommendations are being introduced to minimise the risk of serious hypersensitivity reactions with ferumoxytol. These include a contraindication in patients with any drug allergies and changes in the method of administration—see article A1.

Before starting denosumab treatment, a dental examination and appropriate preventive dentistry are now recommended to reduce the risk of osteonecrosis of the jaw (ONJ). This applies to all patients considered for denosumab 120 mg for cancer and to patients with ONJ risk factors considered for denosumab 60 mg for osteoporosis. Monitor calcium levels before and during treatment as described in the updated recommendations below to reduce the risk of hypocalcaemia—see article A2.

Nitrofurantoin is now contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m^2. However, a short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30 to 44 ml/min/1.73m^2—see article A3.

We are publishing new guidelines for reporting suspected adverse drug reactions (ADRs) in children and adolescents aged under 18 years via the Yellow Card Scheme. The advice on which suspected ADRs to report in children is now the same as for adults. Please complete a Yellow Card for all suspected ADRs in children that are serious, result in harm, or are associated with new drugs and vaccines (identified by the black triangle symbol: ▼)—see article Y1.

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Drug safety advice

A1 Ferumoxytol: risk of serious hypersensitivity reactions—contraindicated if any drug allergy; administer via infusion

New recommendations are being introduced to minimise the risk of serious hypersensitivity reactions with ferumoxytol. These include a contraindication in patients with any drug allergies and changes in the method of administration (see below)

Hypersensitivity reactions are known to occur rarely with all intravenous (IV) iron products and may be life-threatening. Recommendations to manage and minimise this risk were strengthened in 2013 following an EU review (see Drug Safety Update article from August 2013).

Drug Safety Update article from August 2013
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON300398

Risk of hypersensitivity reactions with ferumoxytol

Ferumoxytol (Rienso) was approved in the EU in June 2012 for the IV treatment of iron deficiency anaemia in adults with chronic kidney disease.

The European Medicines Agency has re-evaluated the benefits and risks of ferumoxytol. The evaluation focused on the cumulative reports of serious hypersensitivity reactions—including life-threatening and fatal anaphylactic reactions—to ferumoxytol since it was first approved for use in the USA in 2009 (see Drug Safety Update article from June 2014). Many of the patients who had a life-threatening or fatal anaphylactic reaction also had a known history of drug allergy to a non-iron product (eg, an antibiotic). New recommendations for ferumoxytol are being introduced as a result of this re-evaluation:

Drug Safety Update article from June 2014
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON426906

Advice for healthcare professionals:

Prescribing

- Ferumoxytol is now contraindicated in patients with any known history of drug allergy, including hypersensitivity to other parenteral iron products.
- As with all IV iron products, the risk of hypersensitivity is increased in patients with immune or inflammatory conditions (eg, systemic lupus erythematosus, rheumatoid arthritis) and in patients with a history of severe asthma, eczema, or other atopic allergy. In these patients, ferumoxytol should only be used if the benefits are clearly judged to outweigh the risks.

Administration

- Ferumoxytol should only be administered as an intravenous infusion, in 50 to 250 ml of sterile 0.9% sodium chloride or sterile 5% glucose, and over a minimum period of 15 minutes. Do not administer by injection.
- Place patients in a reclining or semi-reclining position during the ferumoxytol infusion and for at least 30 minutes thereafter.
- Carefully monitor patients for signs and symptoms of hypersensitivity reactions, including monitoring of blood pressure and pulse, during and for at least 30 minutes after the infusion.
- As with all IV iron products, ferumoxytol should only be administered when resuscitation facilities and staff trained to evaluate and manage anaphylactic or anaphylactoid reactions are immediately available.

Information for patients

- Tell patients to immediately inform their healthcare practitioner if they start to feel unwell during or after their ferumoxytol infusion.
- As with all IV iron products, patients should be informed of the risk and potential seriousness of a hypersensitivity reaction before every administration of ferumoxytol.

Further information
Letter sent to healthcare professionals in August 2014
http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con454358.pdf

Reporting of suspected adverse drug reactions

- Please continue to report suspected adverse reactions to any IV iron product, including ferumoxytol, to us on a Yellow Card. Please include the name of the specific product administered (www.mhra.gov.uk/yellowcard).

Article citation: Drug Safety Update September 2014 vol 8, issue 2: A1.

A2 **Denosumab: minimising the risk of osteonecrosis of the jaw; monitoring for hypocalcaemia—updated recommendations**

Denosumab is associated with a risk of osteonecrosis of the jaw (ONJ) and with a risk of hypocalcaemia. Before starting denosumab treatment, a dental examination and appropriate preventive dentistry are now recommended to reduce the risk of osteonecrosis of the jaw (ONJ). This applies to all patients considered for denosumab 120 mg for cancer and to patients with ONJ risk factors considered for denosumab 60 mg for osteoporosis (see below). Tell patients to maintain good oral hygiene and report any oral symptoms.

The risk of hypocalcaemia increases with the degree of renal impairment. Monitor calcium levels depending on the indication as described below and tell patients to report symptoms of hypocalcaemia (see advice below)

Denosumab 120 mg solution for injection (Xgeva▼) is given once every 4 weeks to prevent skeletal related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with bone metastases from solid tumours.

Denosumab 60 mg solution for injection (Prolia) is given once every 6 months to treat osteoporosis in postmenopausal women at increased risk of fractures. It is also indicated for treatment of bone loss associated with hormone ablation in men with prostate cancer who are at high risk of fractures.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a well-known and common side effect in patients receiving denosumab 120 mg for cancer. Risk factors for ONJ include:

- smoking
- old age
- poor oral hygiene
- invasive dental procedures (eg, tooth extractions, dental implants, oral surgery)
- comorbidity (eg, dental disease, anaemia, coagulopathy, infection)
- advanced cancer
- previous treatment with bisphosphonates
- concomitant treatments (eg, chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck)

In clinical trials, ONJ incidence increased with duration of denosumab 120 mg exposure. The patient-year adjusted incidence of confirmed ONJ was 1.1% in the first year of treatment, 3.7% in the second year, and 4.6% per year thereafter. Patients with certain dental risk factors (eg, history of ONJ, unhealed oral surgery) were excluded from these trials.

There have been rare cases of ONJ in patients receiving denosumab 60 mg for osteoporosis in clinical practice. The most common risk factors were invasive dental procedures, history of bisphosphonate therapy, and being more than 65 years old.

To date, we have received 9 Yellow Card reports[1] of ONJ in patients receiving denosumab 120 mg, 12 reports in patients receiving denosumab 60 mg, and 5 reports in patients receiving an unspecified dose of denosumab.

1. Yellow Card reports are reports of suspected adverse drug reactions (ADRs) submitted voluntarily by healthcare professionals and members of the public in the UK. The number of reports received should not be used to determine the incidence of an ADR. This is because neither the total number of ADRs occurring, nor the number of patients using the drug is known. ADR reporting rates are influenced by the seriousness of ADRs, their ease of recognition, and the extent of use of a particular drug, and may be stimulated by publicity about a drug.

Based on this evidence, the recommendations regarding the need for a dental examination and appropriate preventive dentistry before treatment have been updated as described below.

Drug Safety Update article from October 2012
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199560

Hypocalcaemia
Denosumab is also associated with a risk of hypocalcaemia. This risk increases with the degree of renal impairment (see Drug Safety Update article from October 2012). Hypocalcaemia usually occurs in the first weeks of denosumab treatment, but it can also occur later. Therefore the recommendations for calcium monitoring have been updated as described below.

To date, we have received 23 Yellow Card reports[1] of hypocalcaemia in patients receiving denosumab 120 mg, 37 reports in patients receiving denosumab 60 mg, and 6 reports in patients receiving an unspecified dose of denosumab.

Advice for healthcare professionals:

Osteonecrosis of the jaw

The following precautions are now recommended to reduce the risk of ONJ:

Denosumab 120 mg (cancer indication)

- A dental examination and appropriate preventive dentistry before starting denosumab 120 mg are now recommended for all patients.
- Do not start denosumab 120 mg in patients with a dental or jaw condition requiring surgery, or in patients who have not recovered following oral surgery.

Denosumab 60 mg (osteoporosis indication)

- Check for ONJ risk factors before starting denosumab 60 mg. A dental examination and appropriate preventive dentistry are now recommended for patients with risk factors.

Tell all patients to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist.

Hypocalcaemia

Calcium levels should now be monitored as follows:

Denosumab 120 mg (cancer indication)

- Check calcium levels:
  - before the first dose
  - within two weeks after the initial dose
  - if suspected symptoms of hypocalcaemia occur.
- Consider monitoring calcium levels more frequently in patients with risk factors for hypocalcaemia (eg, severe renal impairment, creatinine clearance <30 ml/min).

Denosumab 60 mg (osteoporosis indication)

- Check calcium levels:
  - before each dose
  - within two weeks after the initial dose in patients with risk factors for hypocalcaemia (eg, severe renal impairment, creatinine clearance <30 ml/min)
  - if suspected symptoms of hypocalcaemia occur.

Tell all patients to report symptoms of hypocalcaemia to their doctor (eg, muscle spasms, twitches, or cramps; numbness or tingling in the fingers, toes, or around the mouth).

Further information:
Letters to healthcare professionals sent in August 2014 – includes advice on ONJ and hypocalcaemia that was previously in the summary of product characteristics and has not been changed, as well as the new advice above
Desnosumab 60 mg:
http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con454359.pdf
Denosumab 120 mg:
http://www.mhra.gov.uk/home/groups/comms-ic/documents/drugsafetymessage/con454360.pdf

Article citation: Drug Safety Update September 2014 vol 8, issue 2: A2.

A3 **Nitrofurantoin now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m^2**

Nitrofurantoin is now contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m^2. However, a short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30 to 44 ml/min/1.73m^2. Only prescribe to such patients to treat lower urinary tract infection with suspected or proven multidrug resistant pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects. This contraindication allows nitrofurantoin to be used in patients for whom it was previously not recommended (see below)

Nitrofurantoin is an oral antibiotic for the treatment and prevention of urinary tract infections. The antibacterial efficacy in this infection depends on the renal secretion of nitrofurantoin into the urinary tract. In patients with renal impairment, renal secretion of nitrofurantoin is reduced. This may reduce the antibacterial efficacy, increase the risk of side effects (eg, nausea, vomiting, loss of appetite), and may result in treatment failures.

Nitrofurantoin was previously contraindicated in patients with a creatinine clearance of less than 60 ml/min. We have reviewed the evidence for this contraindication in the context of increasing antibiotic resistance of lower urinary tract pathogens to standard therapy (trimethoprim and amoxicillin). We also considered the risk of *Clostridium difficile* colitis associated with the widespread use of alternative broad-spectrum antibiotics (cephalosporins and flouroquinolones). We concluded that the existing contraindication is no longer supported and that the available evidence[1,2] justified a revised contraindication against use in patients with an eGFR of less than 45 ml/min/1.73m^2.

We remind you that antibiotic treatment of asymptomatic bacteriuria is not advised except during pregnancy and other special circumstances.

1. Geerts AF, et al. *Eur J Clin Pharmacol* 2013; **69**(9):1701–7.
2. Oplinger M, et al. *Ann Pharmacother* 2013; **47**(1):106–11.

Advice for healthcare professionals:

- Nitrofurantoin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m^2.
- Nitrofurantoin should not be used to treat sepsis syndrome secondary to urinary tract infection or suspected upper urinary tract infections
- A short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30 to 44 ml/min/1.73m^2. Only prescribe to such patients to treat lower urinary tract infection with suspected or proven multidrug resistant pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects.
- Consider checking renal function when choosing to treat with nitrofurantoin, especially in the elderly.
- Closely monitor for signs of pulmonary, hepatic, neurological, haematological, and gastrointestinal side effects during treatment, as previously advised in the summary of product characteristics (see left).
- Consult official guidance on the appropriate use of antibiotics when prescribing nitrofurantoin.

Further information:
Nitrofurantoin summary of product characteristics
http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/?IdcService=SS_GET_PAGE&nodeId=%3C%25%3D+nodeId+%25%3E&searchFiled=nitrofurantoin

Article citation: Drug Safety Update September 2014 vol 8, issue 2: A3.

Yellow Card Scheme update

Black triangle scheme: http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/BlackTriangleproducts/index.htm]

Further guidance on what to report: www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/Informationforhealthcareprofessionals/Whattoreport/index.htm

Y1 **New guidance on reporting suspected adverse drug reactions in children**

We are publishing new guidelines for reporting suspected adverse drug reactions (ADRs) in children and adolescents aged under 18 years via the Yellow Card Scheme. The advice on which suspected ADRs to report in children is now the same as for adults (ie, we are no longer requesting all suspected ADRs to be reported for children):

Yellow Card reporting guidelines for ADRs in adults or children
Please complete a Yellow Card for:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
- all suspected ADRs associated with new drugs and vaccines (identified by the black triangle symbol: ▼)

This new guidance responds to feedback that the previous guidelines—asking all suspected ADRs in children to be reported—were impractical and deterred reporting. If you are in any doubt as to whether a suspected ADR was serious or harmful, please complete a Yellow Card anyway.

Importance of reporting paediatric ADRs
Watch out for suspected ADRs in children and neonates, which can be different from those in adults. Knowledge about ADRs in children is less well established because:

- action of a drug and its pharmacokinetics in children (especially in the very young) may be different from that in adults;
- drugs may not have been extensively tested in children;
- many drugs are not specifically licensed for use in children and are used either 'off-label' or as unlicensed products;
- drugs may affect the way a child grows and develops or may cause delayed adverse reactions which do not occur in adults;
- suitable formulations may not be available to allow precise dosing in children or they may contain excipients that should be used with caution in children;
- the nature and course of illnesses and adverse drug reactions may differ between adults and children.

Call for reporting
Please continue to use Yellow Cards to report suspected ADRs to medicines, vaccines, and herbal or complementary products, whether self-medicated or prescribed. Yellow Cards should also be completed for suspected ADRs associated with misuse, overdose, or from use of unlicensed or off-label medicines. ADRs where harm occurs to the patient as a result of a medication error are also reportable as a Yellow Card or through the local risk management systems into the National Reporting and Learning System (NRLS). If reported to the NRLS, these will be shared with the MHRA. If the NRLS is not available and harm occurs, report using a Yellow Card.

The quickest way to send a Yellow Card is via our website: www.mhra.gov.uk/yellowcard

Further guidance on what to report can be found on our 'what to report' page (see left).

Article citation: Drug Safety Update September 2014 vol 8, issue 2: Y1.

S1 Domperidone: risk of cardiac side effects– no longer available without prescription

Domperidone is a dopamine antagonist with antiemetic properties. It should no longer be sold to anyone without a prescription. It is associated with a small increased risk of serious cardiac side effects (eg, QTc prolongation, torsade de pointes, serious ventricular arrhythmia, and sudden cardiac death). Therefore people need to have a medical assessment before taking domperidone to determine if it is suitable for them.

Figure: A recall has been issued for non-prescription domperidone (Motilium 10 and Motilium instants)

Advice for healthcare professionals:

- Domperidone must not be sold without prescription
- A recall has been issued for non-prescription domperidone (Motilium 10 and Motilium instants)
- Take into account the updated prescription advice before prescribing domperidone (see Drug Safety Update article from May 2014)

Advice to give to patients

- If you have recently bought domperidone without a prescription and you wish to continue taking it, speak to your doctor or pharmacist at your next routine visit. There is no problem if you wish to stop and a healthcare professional can advise on suitable alternatives for nausea and vomiting.
- If you have been prescribed domperidone, there is no need to stop taking it. Speak to your doctor or pharmacist at your next routine visit if you have any heart problems or other concerns about the treatment.
- Talk to a doctor straight away if you experience dizziness; fainting; chest pain; or a rapid, fluttering, or pounding heartbeat while taking domperidone.

Drug Safety Update article from May 2014
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON418518

Further information
Drug alert
https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=102218

MHRA press release
http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON452546

Pharmacovigilance Risk Assessment Committee (PRAC) assessment report
http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Domperidone_31/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500168926.pdf

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