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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First, we communicate new advice for febuxostat for hyperuricaemia following clinical trial results showing an increased risk of cardiovascular death and increased all-cause mortality, compared with allopurinol, in patients with gout and major cardiovascular disease (page 2). Febuxostat should be avoided in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate.

Second, we advise of a rare risk of serious liver injury including cases requiring transplantation, with tocilizumab for rheumatological indications. Liver function should be monitored before starting treatment and every 4–8 weeks for the first 6 months of treatment with tocilizumab, followed by every 12 weeks thereafter (page4). These recommendations do not apply when tocilizumab is used for cytokine release syndrome (CRS).

Next, on page 7, we remind prescribers and those dispensing rivaroxaban that 15 mg or 20 mg tablets should be taken with food. This reminder follows a small number of UK reports suggesting lack of efficacy (thromboembolic events) in patients taking 15 mg or 20 mg rivaroxaban on an empty stomach.

Finally, see pages 8, 9, and 10 for the latest letters and alerts sent to healthcare professionals, including information about the permanent discontinuation of Myocrisin (Sodium aurothiomalate) Solution for Injection, also known as GOLD injections.

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Febuxostat (Adenuric): increased risk of cardiovascular death and all-cause mortality in clinical trial in patients with a history of major cardiovascular disease

Avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate. Findings from a phase 4 clinical study (the CARES study) in patients with gout and a history of major cardiovascular disease show a higher risk for cardiovascular-related death and for all-cause mortality in patients assigned to febuxostat than in those assigned to allopurinol.

Advice for healthcare professionals:

- avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate.
- note the clinical guidelines for gout (see below), which recommend treatment with febuxostat only when allopurinol is not tolerated or contraindicated
- report suspected adverse drug reactions to febuxostat on a Yellow Card

The CARES study

Design of the CARES study

ClinicalTrials ID NCT01101035

The CARES study was a phase 4, randomised, double-blind, non-inferiority trial that recruited patients with gout and a history of major cardiovascular disease from the USA, Canada and Mexico.[1]

1. White WB, et al. CARES investigators. *N Engl J Med* 2018; 378: 1200–10.

The primary endpoint was time to first occurrence of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and unstable angina with urgent coronary revascularisation. Outcomes analysis was for patients who had received at least 1 dose of the randomly allocated treatment.

Findings of the CARES study

Overall 57% of patients prematurely discontinued trial treatment and 45% of patients did not complete all trial visits; 6,190 patients were followed for a median of 32 months. The median duration of exposure was 728 days for patients in febuxostat group (n=3,098) and 719 days in allopurinol group (n=3,092).

The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% versus 10.4% of patients, respectively; hazard ratio 1.03, 95% confidence interval [CI] 0.87–1.23).

In secondary analysis, the incidence of cardiovascular deaths was higher in the group assigned to febuxostat than in the group assigned to allopurinol (4.3% versus 3.2%, respectively; hazard ratio 1.34, 95% CI 1.03–1.73). The incidence of all-cause mortality was also higher in patients assigned to febuxostat than in those assigned to allopurinol (7.8% versus 6.4% respectively; hazard ratio 1.22, 95% CI 1.01–1.47), which was mainly driven by the higher rate of cardiovascular deaths in the febuxostat group. For other findings of the trial, see published findings.[1]

EU review of risk following CARES study

An EU review of the findings of the CARES study and their impact on the safety of febuxostat has recommended avoiding febuxostat in patients with a history of major cardiovascular disease. The Summary of Product Characteristics and Patient Information Leaflet is being updated to reflect the CARES study results.

Letter to healthcare professionals

The European phase 4 FAST study is evaluating the cardiovascular safety of febuxostat and allopurinol.[2] An independent Data Monitoring Committee has regularly reviewed and assessed unblinded data from the FAST study and has the authority to discontinue the study based on evaluation of benefits and risks. The results of the FAST study are expected in 2020.

2. MacDonald TM, et al. *BMJ Open* 2014; 4: e005354.

Patients taking febuxostat are advised to contact their healthcare professional if they are concerned about their medicine.

About febuxostat

Febuxostat, at doses of 80 mg and 120 mg, is indicated for treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence, of tophus or gouty arthritis). Febuxostat at a dose of 120 mg is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome.

Clinical guidelines recommend febuxostat for chronic hyperuricaemia or gout when allopurinol is not tolerated or contraindicated.[a,b,c] Data from the past 3 years suggest a steady increase in use of febuxostat in the UK, with usage approximately 19,000 patient-years in 2018.[3]

3. Data derived from IQVIA MIDAS Q1 2016 to Q4 2018, by the MHRA, February 2019. Patient-years estimated from the data by using defined daily doses (DDD) as provided by WHO.

Report via Yellow Card

As for all medicines, MHRA will continue to monitor the benefit and risks of febuxostat. Please continue to report any suspected adverse drug reaction via the Yellow Card Scheme. Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card. Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card app.

You can also use the app to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges.

Download the Yellow Card App today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices.

Article citation: Drug Safety Update volume 12, issue 12: July 2019: 1.

Footnotes

a. British National Formulary. Febuxostat, National funding/access decisions. Version accessed May 2019.
b. National Institute for Health and Care Excellence. Gout. Clinical Knowledge Summary. Version accessed May 2019. Last revised in February 2018.
c. Scottish Medicines Consortium. Febuxostat in chronic hyperuricaemia. Version accessed May 2019. Last revised in September 2010. Treatment with febuxostat for chronic hyperuricaemia is restricted to use in conditions when urate deposition has already occurred and when treatment with allopurinol is inadequate, not tolerated or contraindicated.

Tocilizumab (RoActemra): rare risk of serious liver injury including cases requiring transplantation

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be measured before starting treatment with tocilizumab and monitored every 4–8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter. Serious liver injury has been reported on treatment with tocilizumab from 2 weeks to more than 5 years after initiation.

Advice for healthcare professionals:

- rare but serious cases of drug-induced liver injury, including acute liver failure and hepatitis, have been reported in patients treated with tocilizumab; some cases required liver transplantation
- advise patients to seek medical help immediately if they experience signs and symptoms of liver injury, such as tiredness, abdominal pain, and jaundice
- monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at initiation, every 4–8 weeks during the first 6 months of treatment, and every 12 weeks thereafter in patients with rheumatological indications
- exercise caution when considering treatment initiation in patients with ALT or AST higher than 1.5-times the upper limit of normal (ULN); initiation of treatment is not recommended in patients with ALT or AST higher than 5-times the ULN (see table below)
- if liver enzyme abnormalities are identified, consult the dose modifications recommended, which have not changed (see below)
- report any suspected adverse reactions associated with tocilizumab to the Yellow Card Scheme

Review of reports of serious liver injury

Tocilizumab is known to cause transient or intermittent mild to moderate elevation of hepatic transaminases, with increased frequency when used in combination with potentially hepatotoxic drugs (for example, methotrexate). A recent EU cumulative review found that, in rare cases, treatment was associated with severe liver injury.

The review of data from clinical trials, non-interventional studies, spontaneous reports, and the published literature identified 8 cases of tocilizumab-related drug-induced liver injury worldwide, including acute liver failure, hepatitis, and jaundice.

At the time of publication, worldwide exposure for tocilizumab is estimated to be more than 1 million patient-years.

Details of reports

These events occurred on treatment with tocilizumab at between 2 weeks and more than 5 years after initiation, with a median latency of 98 days. Two cases of acute liver failure required liver transplantation.

In one case, increased liver function test enzymes were seen after 2 weeks of tocilizumab treatment, with drug-induced liver injury diagnosed approximately 6 weeks after treatment initiation. It is noted that this patient had previously experienced increased liver function test enzymes with certolizumab pegol.

Of the remaining cases, 4 reports had an onset time of roughly 3–4 months. In another case, the patient began tocilizumab treatment and had normal liver function test results for approximately 18 months before the onset of symptoms of liver dysfunction. 1 patient was noted to have normal liver function before starting tocilizumab and then elevated liver function test enzymes at routine testing 5 years later. In the final case, the time to onset was not reported.

Letter to healthcare professionals

These reports of serious liver injury are considered to be rare and the benefit-risk profile of tocilizumab in the approved indications remains favourable. A letter has been sent to healthcare professionals to advise them of this information.

Recommended liver monitoring

In patients with rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis receiving tocilizumab, monitor alanine aminotransferase (ALT) or aspartate aminotransferase (AST) every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter.

As per the current prescribing information, continue to exercise caution when considering initiation of tocilizumab treatment in patients with ALT or AST higher than 1.5-times ULN. Tocilizumab treatment is not recommended in patients with elevated ALT or AST levels higher than 5 times the upper limit of normal (ULN).

Advise patients to immediately seek medical help if they experience signs and symptoms of hepatic injury, such as tiredness, abdominal pain, or jaundice.

Please note, these updates do not apply to the indication for treatment of cytokine release syndrome (CRS).

Background

Tocilizumab (brand name RoActemra) is an interleukin inhibitor indicated for the treatment, in combination with methotrexate, of rheumatoid arthritis, giant cell arteritis in adult patients [subcutaneous formulation only], polyarticular juvenile idiopathic arthritis (in patients 2 years of age and older), and systemic juvenile idiopathic arthritis.

RoActemra can be given as monotherapy in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate.

RoActemra is also indicated for the treatment of chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients 2 years of age and older [intravenous formulation only].

Dose adjustments due to liver enzyme abnormalities

The dose adjustments due to liver enzyme abnormalities remain the same as those advised in the current product information. For ease of reference, these are recorded in the table below.

Laboratory value of ALT or AST	Action in patients with rheumatoid arthritis and giant cell arteritis treated with pre-filled pens or syringes	Action in patients with rheumatoid arthritis and giant cell arteritis treated with infused solution	Action in patients with polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis
1–3-times ULN	Modify the dose of concomitant disease-modifying anti-rheumatic drugs (for rheumatoid arthritis) or immunomodulatory agents (giant cell arteritis) if appropriate. For persistent increases in this range, reduce tocilizumab dose frequency to every other week injection or interrupt tocilizumab until ALT or AST have normalised. Restart with weekly or every other week injection, as clinically appropriate	Modify the dose of the concomitant methotrexate if appropriate. For persistent increases in this range, reduce tocilizumab dose to 4 mg/kg or interrupt tocilizumab until ALT or AST have normalised. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate	Modify the dose of the concomitant methotrexate if appropriate. For persistent increases in this range, interrupt tocilizumab until ALT or AST have normalised
3–5-times ULN	Interrupt tocilizumab dosing until lower than 3-times ULN and follow recommendations for ALT/AST 1–3-times ULN. For persistent increases higher than 3 times the ULN (confirmed by repeat testing), discontinue tocilizumab	Interrupt tocilizumab dosing until lower than 3-times ULN and follow recommendations above for 1–3-times ULN. For persistent increases higher than 3-times ULN, discontinue tocilizumab	Modify the dose of the concomitant methotrexate if appropriate. Interrupt tocilizumab dosing until lower than 3-times the ULN and follow recommendations for 1–3-times ULN
Higher than 5-times ULN	Discontinue tocilizumab	Discontinue tocilizumab	Discontinue tocilizumab. The decision to discontinue tocilizumab in polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis for a laboratory abnormality should be based on the medical assessment of the individual patient

Report any suspected adverse drug reactions

Please continue to report suspected adverse drug reactions (ADRs) to the Yellow Card Scheme. Reporting suspected ADRs, even those known to occur, adds to knowledge about the frequency and severity of these reactions and can be used to identify patients who are most at risk. Your report helps the safer use of medicines.

Article citation: Drug Safety Update volume 12, issue 12: July 2019: 2.

Rivaroxaban (Xarelto▼): reminder that 15 mg and 20 mg tablets should be taken with food

MHRA has received a small number of reports suggesting lack of efficacy (thromboembolic events) in patients taking 15 mg or 20 mg rivaroxaban on an empty stomach; remind patients to take 15 mg or 20 mg rivaroxaban tablets with food.

Advice for healthcare professionals:

- remind patients to take rivaroxaban 15 mg or 20 mg tablets with food
- for patients who have difficulty swallowing, tablets can be crushed and mixed with water or apple puree immediately before taking; this mixture should be immediately followed by food
- rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food
- report suspected adverse drug reactions, including any suspected events associated with lack of efficacy to rivaroxaban, on a Yellow Card

Importance of taking rivaroxaban 15 mg and 20 mg tablets with food

Clinical trials of rivaroxaban showed that food intake does not affect absorption of 2.5 mg or 10 mg tablets, while absorption of 20 mg tablets was optimal when taken with high-fat, high-calorie meal. For this reason, rivaroxaban 15 mg and 20 mg tablets are to be taken with food.

MHRA has received a small number of reports of patients taking rivaroxaban 15 mg or 20 mg who experienced a thromboembolic event, which the reporter suspected was due to the patient taking the tablets on an empty stomach.

The section of the Patient Information Leaflet for rivaroxaban 15 mg and 20 mg tablets that advises patients how to take their medicine has been revised to emphasise patients must take rivaroxaban with a meal and the tablets should be swallowed preferably with water.

Further information about rivaroxaban

Xarelto (rivaroxaban) is a direct inhibitor of coagulation factor Xa with the following indications:

- co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (2.5 mg)
- co-administered with ASA, for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (2.5 mg)
- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (10 mg)
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age of 75 years and older, diabetes mellitus, prior stroke or transient ischaemic attack (15 mg and 20 mg)
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (10 mg, 15 mg, and 20 mg).

Article citation: Drug Safety Update volume 12, issue 12: July 2019: 3.

Letters and drug alerts sent to healthcare professionals in June 2019

Myocrisin permanent discontinuation

In June 2019, healthcare professionals were informed of the permanent discontinuation of Myocrisin (Sodium aurothiomalate) Solution for Injection, also known as GOLD injections (see letter to healthcare professionals). This discontinuation is due to a shortage of active pharmaceutical ingredient (API) and is not due to any safety issue.

No new patient should commence treatment with Myocrisin injection. Prescribers should complete arrangements to transfer patients on Myocrisin to suitable therapeutic alternatives under medical supervision.

Other letters

In June 2019, the following letters were sent to healthcare professionals:

- Cerliponase alfa (Brineura▼): temporary change in packaging
- Darzalex▼(daratumumab) and risk of reactivation of hepatitis B virus
- Retinoids▼ (Acitretin, Adapalene, Alitretinoin, Bexarotene, Isotretinoin, Tretinoin, and Tazarotene): risk of teratogenicity and neuropsychiatric disorders
- Febuxostat (Adenuric): increased risk of cardiovascular death and all-cause mortality in patients treated with febuxostat in the CARES study

Drug alerts

In June 2019, the following drug alerts were issued:

FMD Alert: Class 2 (MDR 123-05/19). Issued 27 June 2019. Medicines have been taken out of the regulated medicines supply chain during distribution. The products have been parallel imported into the UK by B & S Healthcare from Italy and have been re-labelled in B & S Healthcare livery. See alert for list of products and batch numbers.
The 3 products that are being recalled to patient level are Clexane 8000iu Injection 0.8ml; Neupro 4mg/24 hr patches; and Vimpat 100mg tablets. The products being recalled at pharmacy level are Dovobet Gel, Incruse Inhaler, Provisacor (Crestor) 10mg Tablets, Seebri Breezhaler, and Spiriva Inhalation Powder.

Class 2 Medicines Recall – Paracetamol 500mg Tablets, 1 x 1000 PL 04077/0001 (MDR 13-04/19). Issued 13 June 2019. Batches listed in the alert are being recalled because a small number of pots from each batch have been found to contain discoloured tablets due to fungal contamination.

Company led drug alert – Docetaxel Injection 160mg /16ml and Docetaxel Injection 20mg / 2ml. Issued 24 June 2019. Batches listed in the alert are being recalled after routine stability testing identified that levels of a known impurity, 10-oxo-docetaxel, may exceed the acceptable level at end of shelf-life.

Class 4 Drug Alert – Baxter Potassium Chloride containing intravenous infusions. Issued 3 June 2019. A small number of infusion bags have been found to be missing red text to highlight the presence of potassium chloride. Infusion bags in inventory should be inspected, and if found to be without the red print (example in alert) should be placed in quarantine. Home patients who use these products should be notified.

Emerade: medicines defect information

Healthcare professionals should also be aware of the Class 4 Medicines Defect Information for Emerade adrenaline auto-injectors, issued 11 July 2019.

Healthcare professionals are asked to contact patients supplied with an Emerade device and their caregivers to reinforce the advice to always carry TWO in-date adrenaline auto-injectors with them at all times (see Drug Safety Update issued in August 2017).

This alert follows detection of a risk of Emerade product failing to deliver a dose of adrenaline from the syringe due to blockage of the needle. For more information, see the alert online.

Patients or their carers who experience any problem with Emerade failing to activate should report this via the MHRA's Yellow Card Scheme and keep the pen for further examination.

Additional advice to reiterate to patients is to:

- Check expiry date and replace the pen before it expires
- Use the auto-injector at first signs of anaphylaxis
- Call 999, ask for an ambulance and say anaphylaxis (pronounced as 'anna -fill-axis')
- Lie flat if possible with your legs up to keep your blood flowing
- Use second pen if still unwell after 5-15 minutes

The chance of a successful outcome is increased if there is prompt administration of adrenaline at the first signs of anaphylaxis. Even with an apparently successful response to adrenaline auto-injector administration, patients may relapse some hours later which underlines the importance that the emergency services should always be called.

Article citation: Drug Safety Update volume 12, issue 12: July 2019: 4.

Medical Device Alerts issued in June 2019

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

Dialog+ haemodialysis machines with software versions 9.xx (excluding versions 9.18, 9.1A, 9.1B) – software and hardware upgrade required (MDA/2019/024). Issued 26 June 2019. Manufactured by B. Braun Avitum AG – Malfunction of the temperature sensor can result in temperature of the dialysis fluid to be more than ±1°C outside the programmed values, which can lead to inadequate treatment.

Article citation: Drug Safety Update volume 12, issue 12: July 2019: 5.