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 inform healthcare professionals that the licence for Esmya (uliprisal acetate 5mg) has been suspended while a review is conducted. The review was initiated following a further case of liver failure requiring a transplant in a patient taking this medicine (page 2). Contact patients currently taking Esmya for uterine fibroids as soon as possible and advise them to stop their treatment

Second, we inform prescribers of tofacitinib for arthritis and ulcerative colitis of new recommendations following a review of increased venous thromboembolism and infection risks with tofacitinib treatment (page 4). Clinicians treating patients with rheumatoid arthritis should also see recommendations on page 7, in which we advise of the known increased risk of deep vein thrombosis or pulmonary embolism with baricitinib and with the new drug in the class upadacitinib.

Next, on page 9, we remind healthcare professionals of the rare risk of diabetic ketoacidosis in patients with diabetes when SGLT2 inhibitors therapy is interrupted. To identify earlier any cases of diabetes ketoacidosis in hospitalised patients, we recommend measuring ketone levels, preferably in blood rather than urine, before SGLT2 inhibitors are restarted.

On page 11, following a report of a recent death, we remind prescribers that benzodiazepines and opioids can both cause life-threatening respiratory depression, which can be additive if they are used together.

Healthcare professionals and members of the public should continue to follow Government advice on novel coronavirus and coronavirus disease (COVID-19). For information about how MHRA is contributing to the essential work needed to protect public health in the UK, see MHRA statement.

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Esmya (ulipristal acetate): suspension of the licence due to risk of serious liver injury

Contact patients currently taking Esmya for uterine fibroids as soon as possible and advise them to stop their treatment. The licence for Esmya has been suspended to protect public health while a safety review is conducted following a further case of liver injury requiring transplant.

Advice for healthcare professionals:

- contact patients currently being treated with Esmya as soon as possible and stop their treatment; discuss alternative treatment options for uterine fibroids as appropriate
- do not start any new patients on Esmya
- advise recent users to seek immediate medical attention if they develop signs and symptoms of liver injury (nausea, vomiting, malaise, right hypochondrial pain, anorexia, asthenia or jaundice)
- perform liver function tests 2–4 weeks after stopping Esmya as recommended in the product information
- report suspected adverse drug reactions without delay to the Yellow Card Scheme
- there are no concerns with emergency contraceptive ellaOne (ulipristal acetate 30mg single dose) at this time

Advice to give to patients

- stop taking Esmya and contact your doctor for advice about other possible treatments for uterine fibroids
- attend appointments for liver function testing after stopping Esmya treatment as advised by your doctor
- seek medical advice immediately if you develop symptoms of liver injury such as abdominal pain, yellowing of the skin or eyes, dark urine, tiredness, loss of appetite, and nausea and vomiting, even if 1–2 months after stopping Esmya treatment
- there are no concerns with emergency contraceptive ellaOne (ulipristal acetate 30mg, single-dose) at this time

Review of serious liver injury

Ulipristal acetate 5mg (Esmya) is authorised for moderate to severe symptoms of uterine fibroids in women who had not reached the menopause.

On 9 March 2020, the European Medicines Agency (EMA) started a review of Esmya following a new case of liver failure requiring liver transplant. This case occurred despite the patient and physician having adhered to measures that were put in place following a previous review to minimise the risk of liver injury, namely measuring liver function before and during treatment, and stopping treatment immediately in case of raised liver enzyme levels.

Drug Safety Update August 2018

This is now the fifth case of liver injury requiring liver transplant reported worldwide in women receiving Esmya.

To protect public health, marketing authorisations for all ulipristal acetate 5mg products for uterine fibroids will be suspended in the UK for the duration of the review. Patients currently taking Esmya for uterine fibroids should stop taking the medicine and no new patients should start treatment. We will communicate the recommendations of the review once finalised.

The MHRA has issued a recall of Esmya from pharmacies, wholesalers, and patients, and the manufacturer will send a letter to UK prescribers and dispensers on 23 March 2020.

Since authorisation and to date, we have received 19 suspected adverse drug reaction reports of liver disorders with the use of Esmya in the UK. None report liver transplant or death. Approximately 2,865 treatment courses of Esmya were dispensed in the UK in 2019.[1]

The emergency contraceptive ellaOne also contains ulipristal acetate (single dose, 30mg). There are no concerns with this medicine at this time.

Report suspected adverse drug reactions

Report without delay any suspected adverse drug reactions (ADRs) associated with Esmya, including signs or symptoms of liver injury, to the Yellow Card Scheme. The Yellow Card Scheme is vital in helping the MHRA to monitor the safety of all healthcare products in the UK to ensure they are acceptably safe for patients and those that use them.

Healthcare professionals, patients, and caregivers can report suspected ADRs via the Yellow Card website or via the Yellow Card app. Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices. You can also view recent alerts from the MHRA and read Drug Safety Updates through the App newsfeed.

Article citation: Drug Safety Update volume 13, issue 8: March 2020: 1.

1 Data derived from IQVIA MIDAS 01/2019 – 12/2019, by the MHRA, March 2020. The assumption was made that each course was 3 months duration, however a patient could take this drug for less than 3 months. It also needs to be taken into consideration, that there is variability in the number of courses a patient will take (between 1 and 4). The number of courses quoted is a broad estimation and therefore is not equivalent to the number of patients who used this product.

Tofacitinib (Xeljanz▼): new measures to minimise risk of venous thromboembolism and of serious and fatal infections

Caution should be used in patients with known risk factors for venous thromboembolism in addition to the underlying disease. Patients older than 65 years of age are at an increased risk of serious infections and should be treated with tofacitinib only if there is no alternative treatment.

Advice for healthcare professionals:

Venous thromboembolism risk

- tofacitinib is associated with a dose-dependent increased risk of serious venous thromboembolism
- use caution in any patients with known risk factors for venous thromboembolism in addition to the underlying disease
- in patients with ulcerative colitis who have known risk factors for venous thromboembolism in addition to the underlying disease, use of 10mg twice-daily tofacitinib for maintenance treatment is not recommended unless no suitable alternative treatment is available
- do not exceed the recommended dose of 5mg twice-daily (or 11mg prolonged-release once-daily) for rheumatoid arthritis or 5mg twice-daily for psoriatic arthritis in any patients

Vigilance for events and actions if they occur

- inform patients of the signs and symptoms of venous thromboembolism before they start tofacitinib and advise them to seek prompt medical help if they develop signs such as a painful swollen leg, chest pain, or shortness of breath
- discontinue tofacitinib treatment permanently if signs of venous thromboembolism occur

Infection risk

- tofacitinib increases the risk of serious and fatal infections, with rates of infections greater in older patients
- only consider use of tofacitinib in patients older than 65 years if no suitable alternative treatment is available

Safety review and interim restrictions

Tofacitinib is authorised for treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis (see Background on page 6). In 2019 interim results from the ongoing study A3921133 prompted a European review into the benefits and risks of tofacitinib. Study A3921133 included patients aged 50 years or older with rheumatoid arthritis and an increased risk of cardiovascular disease.

Drug Safety Update, May 2019

While the review was ongoing, we advised healthcare professionals of the potential risk of venous thromboembolism and temporary contraindications for the 10mg twice-daily dose of tofacitinib in patients with risk factors for pulmonary embolism.

Risk of venous thromboembolism

Following the conclusion of the review, the interim contraindications communicated in May 2019 have been replaced with the measures outlined in this article. A letter has been sent to prescribers and dispensers. Venous thromboembolism is an uncommon reaction with tofacitinib treatment (up to 1 in 100 patents).

Study A3921133 showed an increased risk of pulmonary embolism in this population with tofacitinib 5mg twice daily compared with TNF inhibitors and an even greater risk with 10mg twice-daily (see letter for detailed data). Incidence rates for deep vein thrombosis were also increased with tofacitinib. Risks of pulmonary embolism were further increased in patients with risk factors for venous thromboembolism.

In an ongoing extension trial to assess use of tofacitinib in ulcerative colitis, cases of pulmonary embolism and deep vein thrombosis were also observed in patients using tofacitinib 10mg twice-daily who had underlying venous thromboembolism risk factors.

New recommendations

For any dose and in any indication, exercise caution when considering tofacitinib in patients who have known risk factors for venous thromboembolism, in addition to their underlying disease.

Maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism, unless there is no suitable alternative treatment.

Risk factors for venous thromboembolism include:

- previous venous thromboembolism
- patients undergoing major surgery
- immobilisation
- myocardial infarction (within previous 3 months)
- heart failure
- use of combined hormonal contraceptives or hormone replacement therapy
- inherited coagulation disorder
- malignancy

Other venous thromboembolism risk factors that should be considered include age, obesity (body-mass index ≥30 kg/m^2), diabetes, hypertension, and smoking status.

An increased risk of venous thromboembolism has also been reported with other JAK inhibitors for inflammatory conditions, including baricitinib and upadacitinib (page 7).

Risk of serious and fatal infections

Tofacitinib is known to increase the risk of serious and fatal infections such as pneumonia, cellulitis, herpes zoster, and urinary tract infections. Existing advice contraindicates use of tofacitinib in patients with active infections, and advises healthcare professionals to consider the benefits and risks in patients with recurrent infections, a history of serious or opportunistic infection, or travel to areas of endemic mycoses, and in those who have underlying conditions that may predispose them to infection.

Study A3921133 showed incidence of non-fatal serious infections to be higher in patients with rheumatoid arthritis receiving tofacitinib than in those receiving a TNF inhibitor (see letter for study data). The risk of serious infections and fatal infections was further increased in older patients aged 65 years or older, as compared to younger patients (aged 50–64 years) – see letter for data.

Healthcare professionals are advised only to use tofacitinib in patients older than age 65 years if there is no alternative treatment.

Mortality in rheumatoid arthritis

In the interim analysis of study A3921133 in patients with rheumatoid arthritis, mortality within 28 days of last treatment was increased in patients treated with tofacitinib compared with those treated with TNF inhibitors (see letter for data). Mortality was mainly due to cardiovascular events, infections, and malignancies.

Background

Tofacitinib (Xeljanz▼) was first authorised in the EU in March 2017. It is authorised for the treatment of:

- adults with moderate to severe rheumatoid arthritis or active psoriatic arthritis in patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs
- adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent

Report any suspected adverse drug reactions

Tofacitinib (Xeljanz▼) is a black triangle medicine and any suspected adverse drug reactions (ADRs) should be reported 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 13, issue 8: March 2020: 2.

Baricitinib (Olumiant▼): risk of venous thromboembolism

Discontinue baricitinib treatment permanently if clinical features of deep vein thrombosis or pulmonary embolism occur. Prescribers are reminded to use caution if using baricitinib in patients with risk factors for deep vein thrombosis or pulmonary embolism in addition to rheumatoid arthritis.

Advice for healthcare professionals:

- clinical trial data show a greater frequency of venous thromboembolism events with baricitinib compared with placebo – deep vein thrombosis and pulmonary embolism events are considered to be uncommon with baricitinib (up to 1 in 100 patients)
- use caution if considering baricitinib in patients with additional risk factors for deep vein thrombosis and pulmonary embolism, such as prior medical history of venous thromboembolism, surgery, immobilisation, older age, and obesity
- discontinue baricitinib treatment permanently if clinical features of venous thromboembolism occur
- advise patients undergoing treatment with baricitinib to seek urgent medical attention if they experience a painful swollen leg, chest pain, or shortness of breath
- report any suspected adverse drug reactions associated with baricitinib to the Yellow Card Scheme

Review of risk of venous thromboembolism

Baricitinib (Olumiant▼) is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have responded inadequately to, or who are intolerant, to one or more disease-modifying anti-rheumatic drugs.

In April 2017, clinical trial findings showed an imbalance in cases of deep vein thrombosis and pulmonary embolism with baricitinib treatment compared with placebo. The exposure-adjusted incidence rate for venous thromboembolism was 0 for placebo compared with 1.3 events per 100 patient-years of exposure for baricitinib 4mg. However, at the time a causal link could not be fully established due to the presence of confounding factors. Based on the data, a warning was added to recommend that baricitinib be used with caution in patients with risk factors for deep vein thrombosis and pulmonary embolism and that if patients experience signs of venous thromboembolism, treatment should be temporarily interrupted and patients should be evaluated promptly.

Following findings of an increased risk of pulmonary embolism in an ongoing study with another JAK inhibitor, tofacitinib (see Drug Safety Update on page 4), a recent European cumulative review reassessed the evidence for risk with baricitinib. The advice has now been updated to recommend discontinuation of baricitinib if clinical signs of venous thromboembolism occur.

Details of post-marketing reports of venous thromboembolism

Cumulatively, there have been 102 cases of venous thromboembolism events reported post-marketing worldwide since marketing. Some of these reports contained more than

one thromboembolic event and within these cases there were 63 events of pulmonary embolism and 51 events of deep vein thrombosis.

Cumulatively, as of 31 July 2019, there have been an estimated 95,100 patients exposed to baricitinib and 42,800 patient years of exposure.[1] There was no consistent pattern in time to onset of venous thromboembolism (where provided) but most cases occurred between 6–12 months after initiation.

1. Data provided to MHRA from the manufacturer.

In one case, the patient continued baricitinib treatment after experiencing a deep vein thrombosis. It was later reported that the patient had a recurrent venous thromboembolism and subsequently a pulmonary embolism. Baricitinib treatment was then permanently discontinued.

Upadacitinib – advice for venous thromboembolism

Upadacitinib (Rinvoq▼) was recently approved for use in the EU for the treatment of moderate to severe active rheumatoid arthritis in adults who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs.

Deep venous thrombosis and pulmonary embolism events have been reported in patients taking upadacitinib. Like tofacitinib and baricitinib, upadacitinib should be used with caution in patients at high risk for venous thromboembolism. If features of deep venous thrombosis and pulmonary embolism occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

Report any suspected adverse drug reactions

Baricitinib is a black triangle medicine and any suspected adverse drug reactions should be reported 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 13, issue 8: March 2020: 3.

SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness

SGLT2 inhibitor treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.

Advice for healthcare professionals:

- interrupt sodium-glucose co-transporter 2 (SGLT2) inhibitor treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses
- monitor ketones during this period – measurement of blood ketone levels is preferred to urine
- restart treatment with the SGLT2 inhibitor once ketone values are normal and the patient's condition has stabilised
- report suspected adverse drug reactions to SGLT2 inhibitors to the Yellow Card Scheme

SGLT2 inhibitors: background and risk of diabetic ketoacidosis

Sodium-glucose co-transporter 2 (SGLT2) inhibitors available in the UK are canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin. SGLT2 inhibitors are licensed for use in adults with diabetes to improve glycaemic control.

A detailed European review in 2016 confirmed diabetic ketoacidosis, including euglycaemic diabetic ketoacidosis, as a rare risk for the SGLT2 inhibitor class of medicines. The review recommended healthcare professionals should inform patients on SGLT2 inhibitors of the risks of diabetic ketoacidosis and counsel them on risk factors and actions to take in case of signs and symptoms.

Drug Safety Update, April 2016

Due to the risk of diabetic ketoacidosis, recommendations were added to the product information of these medicines to interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious medical illnesses and to not restart treatment until the patient’s condition has stabilised.

New recommendation to routinely monitor ketones

In 2019 a new European review assessed reports of peri-operative diabetic ketoacidosis in patients taking SGLT2 inhibitors. The review recommended warnings be updated to include routine monitoring of ketones in patients hospitalised for surgery or acute illness. This approach aims to help identify patients who are at risk of developing (or are already in the early stages of) diabetic ketoacidosis, so that prompt corrective measure can be applied.

Testing of ketones in blood is recommended, rather than measuring ketone bodies in urine. The basis for this recommendation is that SGLT2 inhibitors may diminish the excretion of ketone bodies in the urine, thereby making urine measurement of ketone bodies less reliable than blood testing.

The current Joint British Diabetes Society Inpatient Care Group national guideline for the management of diabetic ketoacidosis (2013) already recommends the use of blood ketone tests based on the measurement of β-hydroxybutyrate.

The review of the evidence did not identify a specific type of surgery as being linked to an increased risk of peri-operative diabetic ketoacidosis. In addition, there was insufficient evidence to make specific recommendations concerning peri-operative management such as a specific time-point to stop or restart SGLT2 inhibitor treatment or management of food intake and insulin use.

2016 review of diabetic ketoacidosis

Diabetic ketoacidosis is a serious complication of diabetes caused by low insulin levels. The 2016 EU review was triggered by rare cases of diabetic ketoacidosis in patients taking SGLT2 inhibitors for type 2 diabetes. In several reports of diabetic ketoacidosis assessed by the review, blood glucose levels were only moderately elevated (see EMA's scientific conclusions). Therefore, updates to the product information advised healthcare professionals to test for raised ketones in patients taking SGLT2 inhibitors with signs and symptoms of ketoacidosis, even if plasma glucose levels are near-normal.

The review recommended interrupting SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious illnesses and to not restart treatment until the patient's condition has stabilised. However, the advice did not specifically instruct prescribers to check or monitor ketones. Healthcare professionals were also advised to avoid restarting treatment with a SGLT2 inhibitor in patients who experienced diabetic ketoacidosis during use, unless another cause for the ketoacidosis was identified and resolved.

Report suspected adverse drug reactions on a Yellow Card

Please continue to report relevant suspected adverse drug reactions (ADRs) on a Yellow Card. Reporting suspected ADRs, even those known to occur in association with the medicine, 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.

Healthcare professionals, patients, and caregivers can report suspected ADRs via the Yellow Card website or via the Yellow Card app. Download the app today via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices. You can also view recent alerts from the MHRA and read Drug Safety Updates through the App newsfeed.

Article citation: Drug Safety Update volume 13, issue 8: March 2020: 4.

Benzodiazepines and opioids: reminder of risk of potentially fatal respiratory depression

Benzodiazepines and opioids can both cause respiratory depression, which can be fatal if not recognised in time. Only prescribe together if there is no alternative and closely monitor patients for signs of respiratory depression.

Advice for healthcare professionals:

- benzodiazepines (and benzodiazepine-like drugs) and opioid medicines (opioids) can both cause respiratory depression; when used together, additive effects on the central nervous system increase the risks of sedation, respiratory depression, coma, and death
- only prescribe benzodiazepines (or benzodiazepine-like drugs) and opioids together if there is no alternative
- if a decision is made to co-prescribe, use the lowest doses possible for the shortest duration of time and carefully monitor patients for signs of respiratory depression
- if there is any change in prescribing such as new interactions or dose adjustments, re-introduce close monitoring of the patient
- if co-prescribing methadone with a benzodiazepine or benzodiazepine-like drug, closely monitor for respiratory depression for at least 2 weeks following initiation or changes to prescribing because the respiratory depression effect of methadone may be delayed
- advise patients of the symptoms of respiratory depression and sedation and the need to seek immediate medical attention if these occur
- report suspected adverse drug reactions to any medicines to the Yellow Card Scheme

Reminder of risk of respiratory depression when co-prescribed

The MHRA recently received a report from a Coroner following death by respiratory arrest of a man given the benzodiazepine clonazepam, and among other drugs, the opioid methadone.

We remind healthcare professionals that benzodiazepines and benzodiazepine-like drugs and opioids can both cause respiratory depression. When co-prescribed, the depressive effect on the central nervous system is additive. Therefore, they should only be co-prescribed if there is no alternative. Warnings about the risks of co-prescribing these products were reviewed in Europe in 2018.

Reminder of advice to minimise risk

If co-prescribing of these drugs is considered necessary, the lowest effective doses should be used and for the shortest duration. All patients should be closely monitored. If methadone is prescribed, the respiratory depression effects could be delayed. Monitoring should continue for at least 2 weeks following initiation or changes to prescribing such as increased dose or the addition of a new medicine that may interact with opioids.

Advice to supply to patients

Advise patients to always read the leaflet for the medicines that they have been supplied.

For benzodiazepines or related drugs and opioids, the patient information leaflet advises that these medicines increase the risk of drowsiness, difficulties in breathing (respiratory depression), and coma, and that these effects may be life-threatening. Therefore, patients should seek medical advice if these symptoms occur.

Patients are advised to inform their prescribers about any opioids or sedative medicines they are taking, and to follow any dose recommendation closely. The leaflet advises them that it may be helpful to inform friends or relatives of the signs and symptoms of respiratory depression and sedation and be aware of the need to seek medical attention if they occur.

Report adverse drug reactions on a Yellow Card

Healthcare professionals are asked to report any suspected adverse drug reactions (ADRs) to drugs to the Yellow Card Scheme.

It is easiest and quickest to report ADRs online via the Yellow Cards website or via the Yellow Card app. Download the app via iTunes Yellow Card for iOS devices or via PlayStore Yellow Card for Android devices. You can also view recent alerts from the MHRA and read Drug Safety Updates through the App newsfeed.

Article citation: Drug Safety Update volume 13, issue 8: March 2020: 5.

Letters and drug alerts sent to healthcare professionals in February 2020

Letters from February 2020

- Typhim Vi (Typhoid polysaccharide vaccine): Supply of Standard Export pack
- Mepact 4mg (mifamurtide): Potential for filter leakage or malfunction
- Xeljanz▼ (tofacitinib): increased risk of venous thromboembolism and increased risk of serious and fatal infections

Recall of Emerade 150 microgram adrenaline pens

Class 2 Medicines Recall: **Emerade 150 micrograms** solution for injection in pre-filled syringe, PL 33616/0013 (EL(20)A/14). 4 March 2020.

On 4 March 2020, all unexpired batches of Emerade 150 microgram auto-injectors (pens) were recalled from patients due to an error in one component believed to cause some pens to fail to activate and deliver adrenaline. See the Drug alert for all advice.

Healthcare professionals – doctors, nurses and pharmacists – should ensure patients and carers receive training in correct use of any new adrenaline pen supplied.

Other recalls

Class 2 Medicines recall: Accord-UK Ltd, **Gliclazide 40mg Tablets** (Northstar Livery), PL 20075/0687, (EL (20)A/08). Issued 13 February 2020. All unexpired stock of Gliclazide 40mg Tablets (Northstar Livery) is being recalled from pharmacies and wholesalers as a precautionary measure due to out of specification results for dissolution obtained during routine stability testing.

Class 2 Medicines recall: Medreich PLC, **Ranitidine 150mg Tablets**, PL 21880/0091, Ranitidine 300mg Tablets, PL 21880/0092 (EL (20)A/05). Issued 3 February 2020. All unexpired stock of the ranitidine 150mg and 300mg tablets is being recalled from pharmacies and wholesalers as a precautionary measure due to possible contamination with an impurity N-nitrosodimethylamine (NDMA), which has genotoxic and carcinogenic potential.

Company led drug alert – **Iohexol solution for injection** (350mg/ml and 300mgI/ml). Issued 6 February 2020. Specific batches are being recalled from wholesalers and pharmacies as a precautionary measure due to an out of specification result in the ongoing stability studies.

Class 3 FMD Medicines Recall, **Beconase Aqueous Nasal Spray**, (Beclometasone Dipropionate 50µg), PL 10949/0104, EL (20)A/07. Issued 12 February 2020. There is an issue related to error in the decommissioning of the K84X batch. Although there is no risk to product quality, any remaining stock should be quarantined and returned.

Defect alerts

Class 4 Medicines Defect Information: **Oxylan prolonged-release tablets**, all strengths (oxycodone hydrochloride), (EL (20)/A12). Issued 27 February 2020. The Patient Information Leaflet (PIL) within the packs for the specified batches is missing important safety-relevant text changes about warnings, interactions, and possible side effects. Check product and batch and, if dispensing, ensure that patients are aware of any missing information. The updated PIL is available online.

Class 4 Medicines Defect Information: **Memantine 10mg Film-Coated Tablets,** PL 20416/0260, (EL (20)A/11). Issued 25 February 2020. There is a discrepancy with the product packaging for the listed patched. One side of the pack (end flap) notes an incorrect number of tablets. There is no risk to product quality as a result of this issue and the associated batches are not being recalled at this time; however, exercise caution when dispensing the product.

Class 4 Drug Alert: Crescent Pharma Ltd and Flamingo Pharma (UK) Ltd, **Ibuprofen 400mg** Tablets, (EL (20)A/10). Issued 20 February 2020, updated 24 February 2020. The Patient Information Leaflet within listed batches of pharmacy (P) products contains incorrect dosing instructions. If dispensing these batches, ensure that patients are aware of the correct dosage instructions and follow the maximum daily dose stated on the carton labelling (3 tablets a day [1200mg]).

Class 4 FMD Medicines Defect Information: **Diamorphine Hydrochloride BP 100mg** Lyophilisate for Solution for Injection, PL 20075/0675, (EL (20)A/09). Issued 17 February 2020. The expiry date for the listed batches has not been encoded in 2D data matrix. Attempts to scan the FMD 2D Data Matrix code on the pack will result in an 'Alert' or a failed scan. Perform the usual checks for falsified medicines according to the FMD Source guidance and dispense if deemed acceptable based on these checks.

Class 4 Medicines Defect Information: **Atrolak XL Prolonged-release tablets**, all strengths (quetiapine fumarate). The Patient Information Leaflet (PIL) for all strengths of this product is missing information about possible side effects – Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). If dispensing these batches, ensure that patients are aware of any missing information.

Article citation: Drug Safety Update volume 13, issue 8: March 2020: 6.

Medical Device Alerts issued in February 2020

In this monthly update, we highlight selected Medical Device Alerts and notices 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.

All T34 and T34L (T60) ambulatory syringe pumps – check pumps before each use due to risk of under-infusion and no alarm (MDA/2020/007). Issued 25 February 2020. Manufactured by CME (a BD company) – updated advice to address 'wear and tear' of the syringe pump motor block, which may lead to under-infusion. Inspect the pump before each use and if white plastic debris is present on the lead screw, immediately stop using the pump and send for repair.

Tympanic thermometers – revision of the calibration frequency of Cardinal Health Genius 2 and Genius 3 models. Issued 27 February 2020. Manufactured by Cardinal Health – calibration period revised to 25 weeks instead of yearly to ensure these thermometers remain within their accuracy range and reduce the risk of misdiagnosis or delay in treatment.

t:slim X2 insulin pump – discard or destroy defective mains (A/C) power adapters (MDA/2020/005). Issued 5 February 2020. Manufactured by Tandem Diabetes Care – an exposed component may cause an electrical shock to the user or patient. Identify patients supplied with affected insulin pumps and ensure they receive an replacement adaptor.

Skin preparation electrode gel: recall of all lots of LemonPrep, PediaPrep, Wave Prep and Cardio Prep due to risk of contamination and transmission of infection (MDA/2020/004). Issued 5 February 2020. Manufactured by Mavidon – products may be contaminated with the micro-organism Burkholderia cepacia leading to an infection risk to patients. All products made at this site are being recalled.

Article citation: Drug Safety Update volume 13, issue 8: March 2020: 7.