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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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 of new liver monitoring requirements for cladribine in the treatment of multiple sclerosis. This advice follows uncommon reports of serious liver injury. Liver function should be monitored before each treatment course. Urgently test liver function in patients with symptoms of liver injury, and discontinue or interrupt cladribine treatment in patients with hepatic dysfunction or unexplained increases in liver enzymes. See page 2 for more details.

Second, we remind healthcare professionals that patients on amiodarone treatment for cardiac conditions should be supervised and reviewed regularly (page 5). Amiodarone has been associated with serious and potentially life-threatening side effects, particularly of the lung, liver, and thyroid gland.

Next, we advise that a large study has shown no safety issues of concern relating to the use of metformin during pregnancy (page 8). The licence for metformin now reflects that it can be considered for use during pregnancy and the periconceptional phase as an addition or an alternative to insulin, if clinically needed. This is consistent with current clinical guidance.

On page 10, we summarise recent advice relating to COVID-19 vaccines and medicines published since the February 2022 issue of Drug Safety Update. And on page 11, we include recent letters, recalls, and notifications sent to healthcare professionals about medicines and medical devices.

Cladribine (Mavenclad): new advice to minimise risk of serious liver injury

Liver monitoring requirements for cladribine in the treatment of multiple sclerosis have been introduced following uncommon cases of serious liver injury. Advise patients to seek urgent medical attention if they develop any clinical features of liver dysfunction. Discontinue or interrupt cladribine if significant hepatic injury is confirmed.

Advice for healthcare professionals:

- a small number of cases of clinically significant liver injury have been reported during cladribine treatment for multiple sclerosis
- most events occurred within 8 weeks of the start of the first treatment course of cladribine
- before starting cladribine check if there is a history of liver disorders, including hepatic injury related to other medicines
- monitor liver function tests (including total bilirubin) before each treatment course in years 1 and 2; and, if clinically necessary, during treatment
- urgently check liver function tests (including bilirubin) in patients with symptoms or signs of liver injury
- discontinue or interrupt cladribine treatment in patients with hepatic dysfunction or unexplained increases in liver enzymes
- report any suspected adverse drug reactions associated with cladribine on a Yellow Card

Advice for healthcare professionals to give to patients and carers:

- cladribine treatment for multiple sclerosis has been associated with a risk of serious liver injury – these serious events are uncommon and have most often happened in the 8 weeks after starting the first treatment
- blood tests to check your liver function are needed before the start of each treatment course; you may also need tests during each treatment if your doctor thinks they are needed
- talk to your doctor straight away if you develop any signs of liver problems such as pain in the upper right area of your stomach, yellowing of your skin or the white part of your eyes, loss of appetite, feeling or being sick, dark urine, or widespread itching
- read carefully the Patient Guide from your doctor and the Patient Information Leaflet that accompanies your medicine; keep them handy in case you need to read them again

Cladribine for multiple sclerosis

Cladribine (Mavenclad) is a nucleoside analogue that causes lymphocyte depletion. It is authorised in the UK for the treatment of adults with highly active relapsing multiple sclerosis as defined by clinical or imaging features.

The recommended cumulative dose of cladribine for multiple sclerosis is 3.5mg/kg bodyweight over 2 years, divided into 2 treatment courses of 1.75mg/kg per year. Each treatment course is given over 2 separate weeks: 1 week at the start of the first month and the next week at the start of the following month. Single daily doses are given on 4 or 5 days of each week.

Review of serious liver injury

A recent European review of safety data has identified 16 cases of liver injury post-marketing, including serious cases requiring discontinuation and one fatal case of hepatic failure in a patient with alcohol-related liver disease and who was undergoing tuberculosis treatment with isoniazid. Within the cases of liver injury reviewed, there were rare reports of jaundice and serum transaminase levels greater than 1000 IU/L. However, the majority of cases had mild clinical symptoms.

A small number of cases of liver injury have also been seen in clinical trials. In some of these cases, patients developed significantly increased serum transaminase levels related to treatment. These serious events resolved within 4 months after cladribine was discontinued (in the cases reporting a final outcome). Alternative causes were excluded in one patient, and none required a liver biopsy. Data from clinical trials did not suggest a dose-dependent effect.

Time to onset of liver injury varied, with most cases occurring within 8 weeks after start of the first treatment course. Some patients had underlying hepatic disorders or a history of hepatic injury related to other medicines. A causal mechanism has not been identified.

Updated advice and frequency information

The product information and the educational materials will be revised to include updated advice for healthcare professionals and patients on the risk of serious liver injury. Liver injury will be included as an adverse drug reaction of uncommon frequency (may affect up to 1 in 100 patients). A letter from the manufacturer has also been sent to UK healthcare professionals.

As of 30 June 2021, worldwide, more than 37,600 patients have been treated with Mavenclad in clinical trials and routine clinical practice.[1] In the UK, just under 2200 patients have received Mavenclad since it was marketed in September 2017.

In the UK, up to 25 January 2022, we have received 2 reports of hepatic injury in patients receiving cladribine for multiple sclerosis via the Yellow Card scheme. Both patients developed liver injury within a month of starting cladribine treatment and in one case the alanine aminotransferase (ALT) level exceeded 1000 IU/L. We ask healthcare professionals to continue to be vigilant for suspected adverse drug reactions in UK patients and report any suspected cases (see Reporting instructions on page 4).

Other medicines containing cladribine

Cladribine is also available in other medicines. Leustat injection and Litak 2mg/ml solution for injection are authorised to treat patients with hairy cell leukaemia and Leustat injection is also approved for the treatment of B-cell chronic lymphocytic leukaemia.

Prescribers of these medicines should continue to follow the current recommendations on patient monitoring.

Report suspected reactions on a Yellow Card

Please continue to report suspected adverse drug reactions to the Yellow Card scheme.

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, 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, medical device and test kit incidents used in coronavirus (COVID-19) testing and treatment 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.

Article citation: Drug Safety Update volume 15, issue 8: March 2022: 1.

Footnotes

1. Data provided with the permission of the Marketing Authorisation Holder. February 2022.

Amiodarone (Cordarone X): reminder of risks of treatment and need for patient monitoring and supervision

Amiodarone has been associated with serious and potentially life-threatening side effects, particularly of the lung, liver, and thyroid gland. We remind healthcare professionals that patients should be supervised and reviewed regularly during treatment.

Lung problems may have slow onset but then progress rapidly. Computerised tomography scans may help to confirm a suspected diagnosis of pulmonary toxicity.

Advice for healthcare professionals:

- amiodarone can cause serious adverse reactions affecting the eyes, heart, lung, liver, thyroid gland, skin, and peripheral nervous system
- review regularly patients on long-term amiodarone treatment – some of these reactions may be life-threatening but onset can be delayed
- check liver and thyroid function before treatment, and at 6-monthly intervals; thyroid function should also be monitored for several months after discontinuation
- although routine lung imaging is not necessary in patients taking amiodarone long-term, make patients aware of the need to seek advice if they have new or worsening respiratory symptoms and consider using computerised tomography (CT) scans if pulmonary toxicity is suspected
- report suspected adverse drug reactions associated with amiodarone on a Yellow Card

Advice for healthcare professionals to give to patients and carers:

- amiodarone is used to treat serious heart conditions in which your heart beats unevenly or too fast
- always read the patient information leaflet provided with your medicines and follow the advice on other medicines to avoid and what to do if you have a side effect
- your doctor may perform tests of your blood, lungs, heartbeat, and eyes before and during treatment – it's important to have these tests because they can identify if there's a problem
- stop taking amiodarone and see a doctor or go to a hospital straight away if you experience any of the following during treatment or in the period after stopping amiodarone:
    - new or worsening shortness of breath or coughing that will not go away
    - yellowing of the skin or eyes (jaundice), feeling tired or sick, loss of appetite, stomach pain, or high temperature
    - weakness, weight loss or weight gain, heat or cold intolerance, hair thinning, sweating, changes in menstrual periods, swelling of the neck (goitre), nervousness, irritability, restlessness, or decreased concentration
    - your heartbeat becomes even more uneven or erratic, or becomes very slow
    - any loss of eyesight

Amiodarone and risk of toxicity

Amiodarone is used to treat certain types of abnormal heart rhythm, including atrial fibrillation and tachyarrhythmias. Amiodarone is generally reserved for situations when other treatments cannot be used or have failed. Treatment should be initiated and monitored under hospital or specialist supervision and in accordance with clinical guidance.

Amiodarone is associated with serious adverse effects in several organ systems including the eyes, gastrointestinal tract, nerves, skin, thyroid, lungs, heart, and liver. Amiodarone interacts with many medications, and advice in the relevant section of the Summary of Product Characteristics (SmPC) should be strictly followed.

Amiodarone has a long plasma half-life of around 50 days, meaning that any adverse effects may persist for a month (or more) after treatment has stopped.

The SmPC for amiodarone contains extensive warnings and precautions. Patients must be monitored closely during treatment.

Adverse effects of amiodarone on the lung

Amiodarone can commonly cause lung inflammation (pneumonitis). In some cases, this inflammation can progress to more serious thickening or scarring (fibrosis), which can be life-threatening. Patients should be carefully evaluated clinically, and consideration given to chest X-rays before starting therapy.

Symptoms of pulmonary toxicity can include shortness of breath (which may be severe and unexplained by the current cardiac status), non-productive cough, and general health deterioration (fatigue, weight loss, and fever). Pulmonary toxicity is usually (but not always) reversible following early withdrawal of amiodarone therapy, with or without corticosteroid therapy.

The MHRA has received a report from a Coroner following the death by multi-organ failure of a woman who had been treated with amiodarone for approximately 5 years and who developed pneumonia during treatment. The Coroner raised a concern that there is no requirement for lung imaging to be undertaken when patients are prescribed amiodarone on a long-term basis.

The MHRA has conducted a review of this issue and sought independent expert advice from the Pharmacovigilance and Cardiovascular, Diabetes, Renal, Respiratory and Allergy Expert Advisory Groups of the Commission on Human Medicines.

Updated advice on lung imaging during amiodarone treatment

Experts involved in our review advised that regular lung imaging during treatment may expose patients to excessive radiation, be alarming for patients, and was unnecessary given that patient-reported worsening of respiratory function is usually a good first indicator of pulmonary toxicity. For this reason, it is important that patients know the symptoms of pulmonary toxicity of which to be aware and the fact this can be serious and may happen at any time during treatment (or in the month after stopping treatment).

The Patient Information Leaflet is being updated to emphasise that respiratory symptoms may get progressively worse and can happen at any time after starting treatment. Additionally, the SmPC for healthcare professionals is being updated to emphasise that computerised tomography (CT) scans are more specific than X-rays and may be therefore more helpful in confirming a suspected diagnosis of lung toxicity.

Reminder on thyroid function monitoring

Amiodarone treatment can commonly lead to hypothyroidism or hyperthyroidism, particularly in patients with a personal history of thyroid disorders in whom treatment is contraindicated.

Thyroid-test levels should be checked before starting treatment, at 6-monthly intervals, and for several months following treatment discontinuation. Regular assessment is recommended in patients whose medical history indicates an increased risk of thyroid dysfunction.

Report suspected adverse drug reactions

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 medical device and test kit 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.

Article citation: Drug Safety Update volume 15, issue 8: March 2022: 2.

Metformin in pregnancy: study shows no safety concerns

A large study has shown no safety issues of concern relating to the use of metformin during pregnancy. The licence for metformin now reflects that it can be considered for use during pregnancy and the periconceptional phase as an addition or an alternative to insulin, if clinically needed. This is consistent with current clinical guidance.

Risks of untreated diabetes in pregnancy

Uncontrolled hyperglycaemia in the time around conception (periconceptional phase) and during pregnancy is associated with increased risks to the baby and the patient. Good blood glucose control reduces the risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality.

National guidelines in the UK already recommend metformin for use in diabetes during pregnancy and gestational diabetes if a healthcare professional feels it is appropriate (see guidelines from NICE and SIGN).

Review of new safety data

Following a European review of data from a non-interventional cohort study of population registries in Finland (the CLUE study), the product information for metformin is being updated to permit the use of metformin during pregnancy and the periconceptional phase as an addition or an alternative to insulin, if clinically needed. The Medicines for Women's Health Expert Advisory Group of the Commission on Human Medicines has also reviewed the data from the study and agreed that the product information should be updated.

The study investigated immediate and longer-term effects of exposure to metformin in-utero on children born to patients with pre-existing type 2 diabetes, gestational diabetes, or polycystic ovary syndrome. The results of the study were reassuring, with no safety signals of concern identified for use of metformin in pregnancy relating either to those who were pregnant or their baby.[1]

Among secondary outcomes, similar rates of births that were small (low weight) for gestational age were observed with exposure to metformin and within the group of patients with untreated gestational diabetes. By contrast, an increased risk of small for gestational age was observed with exposure to metformin compared with insulin, which may relate to an overall increase in body weight due to use of insulin.

Updated advice

The advice in the Summary of Product Characteristics for metformin products is being updated. Corresponding changes are also being made to the Patient Information Leaflet. These changes have already been made to the brand-leader Glucophage.

Some fixed-dose combination products containing metformin contain other active substances that should be avoided during pregnancy. The product information for fixed-dose combination products containing metformin will be reviewed and advice on use in pregnancy updated if appropriate.

Advise patients with diabetes mellitus who are pregnant, think they may be pregnant, or are planning to have a baby to speak to their doctor. This is in case any changes are needed to their treatment or monitoring of their blood glucose.

This update to the product information reflects clinical practice and advice in current UK guidelines, including those from NICE and SIGN and resources from the BNF and UKTIS.

Report suspected adverse drug reactions in pregnancy

Report any suspected adverse drug reactions, including adverse pregnancy outcomes, following use of a medicine in pregnancy on a Yellow Card.

For more about the importance of reporting suspected adverse drug reactions associated with medicines in pregnancy, see Drug Safety Update, July 2018.

Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card App (Apple App Store and Google PlayStore).

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 the Yellow Card app.

References

1. Brand KMG, and others. Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. BMJ Open Diabetes Res Care 2022; volume 10: e002363.

Article citation: Drug Safety Update volume 15, issue 8: March 2022: 3.

COVID-19 vaccines and medicines: updates for March 2022

Recent information relating to COVID-19 vaccines and medicines that has been published since the February 2022 issue of Drug Safety Update, up to 11 March 2022.

COVID-19 antivirals: reminder on reporting

We remind of advice in the February 2022 Drug Safety Update on COVID-19 antivirals and reporting to the UK COVID-19 Antivirals Pregnancy Registry.

As the safety of COVID-19 antivirals in pregnancy has not been established, please report any pregnancies which occur during use of a COVID-19 antiviral, including paternal use, to the UK COVID-19 Antivirals Pregnancy Registry. This advice is relevant for molnupiravir (Lagevrio▼), the combination of PF-07321332 (nirmatrelvir) plus ritonavir (Paxlovid▼), and remdesivir (Veklury▼).

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:

- updated the product information for COVID-19 Vaccine Janssen to include dizziness and rare coagulation disorders such as thrombosis with thrombocytopenia syndrome, venous thromboembolism, and immune thrombocytopenia. The storage and transportation instructions have also been updated.

We previously included summaries of latest COVID-19 information, including in the December 2021, January 2022, and February 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.

Article citation: Drug Safety Update volume 15, issue 8: March 2022: 4.

Letters and medicine recalls sent to healthcare professionals in February 2022

Letters

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

- GAMMAGARD S/D 10g (human normal immunoglobulin G (IgG): do not use administration sets supplied with certain batches due to a quality defect associated with sterility; caution required to minimise the risk of infection
- Mavenclad (cladribine): risk of serious liver injury and new recommendations about liver function monitoring. See accompanying Drug Safety Update article on page 2.
- Tisseel Ready to use Solutions for Sealant: supply of batches with incomplete package leaflet technical information section
- Prostin VR Pediatric (alprostadil 500 micrograms/ml concentrate for solution for infusion): temporary supply of unlicensed imported product from the USA

Medicine Recalls and Notifications

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

Class 4 Medicines Defect Information: Flamingo Pharma UK Ltd, Ibuprofen 400mg Tablets, EL (22)A/04. Issued 1 February 2022. A batch of ibuprofen 400mg tablets has been identified that has some cartons with illegible embossed batch numbers. This poses a risk to traceability in the event of a future recall. The batch number on the tablet blisters is clear and there is no issue with product quality. Healthcare professionals should check the blisters before dispensing the affected batch to ensure the batch number can be read.

Company led medicines recall: Bucain Hyperbar 5mg/ml Solution for Injection (unlicensed medicine), CLMR (22)A/01. Issued 14 February 2022. A batch of Bucain Hyperbar (bupivacaine hydrochloride) 5mg/ml Solution for Injection is being recalled by the company. This is a precautionary recall due to out of specification pH results identified during stability testing. This is an unlicensed medicine that is only supplied to hospital pharmacies. Stop supplying the batch immediately, quarantine all remaining stock and return to the UK importer.

Class 2 Medicines Recall: hameln pharma ltd, Water for Injections BP – 100ml vial, EL (22)A 06. Issued 15 February 2022. A batch of Water for Injections 100ml vial is being recalled as a precautionary measure due to out of specification results for pH and conductivity during stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 2 Medicines Recall: Uni Health Distribution, Efudix 5% w/w cream, EL (22)A 07. Issued 17 February 2022. A batch of Efudix (fluorouracil) 5% w/w cream is being recalled from pharmacies as a precautionary measure as cartons may contain Patient Information Leaflets for a different medicine. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier. Healthcare professionals are asked to share an appropriate leaflet with the patient where possible.

Class 2 Medicines Recall: medac GmbH (t/a medac Pharma LLP), Fluorouracil Injection, 50 mg/ml, solution for injection (2500mg/50ml vial), EL (22)A 08. Issued 17 February 2022. Batches of Fluorouracil Injection (5-fluorouracil) 50 mg/ml, solution for injection are being recalled as a precautionary measure due to the presence of glass lamellae particles identified during stability testing. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

UPDATE: Class 4 Medicines Defect Information: Atnahs Pharma UK Limited, Naprosyn Tablets (all strengths), Naprosyn EC 250mg Gastro-Resistant Tablets, Naprosyn EC 500mg Gastro-Resistant Tablets, EL (22)A/09. Issued 23 February 2022. This is an update of the Class 4 Medicines defect information issued on 3 February 2022. Batches of Naprosyn (naproxen) 250mg and 500mg tablets, and Naprosyn (naproxen) EC 250mg and 500mg Gastro-Resistant tablets have been identified to contain Patient Information Leaflets that omit medicine interactions wording for naproxen with aspirin (acetylsalicylic acid). Healthcare professionals dispensing any of the affected batches are asked to provide an updated Patient Information Leaflet. Healthcare professionals should also remind patients to seek medical advice if taking aspirin (acetylsalicylic acid) with Naprosyn Tablets or Naprosyn EC Gastro-Resistant Tablets due to the increased risk of bleeding when these medicines are taken concurrently.

Medical Device Safety Information

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

Surdial X Haemodialysis machine: potential for devices to remove excess fluid outside of machine specification. DSI/2022/002. Issued 17 February 2022. The MHRA is aware of instances of Surdial X haemodialysis machines removing excess fluid via ultrafiltration outside of its specification. There is a small risk of dialysis-induced hypotension in patients who are unable to tolerate excess fluid removal, including patients with poor cardiac function, sepsis, and diabetes with autonomic neuropathy. The manufacturer issued a Field Safety Notice in July 2021 and is continuing to investigate this matter. Actions for heads of renal units, renal nurses, and renal technicians are available in the device safety information.

Stop using Vaginal Speculums with smoke tube and Gynaecological Hysteroscopy sheaths from Gemini Surgical UK: all lots and batches. DSI/2022/001. Issued 17 February 2022. The MHRA has become aware that the Insulated Medium Cusco Speculum with smoke tubes and gynaecological hysteroscopy sheaths from Gemini Surgical UK or Gemini Medical Innovations are being sold with a falsely applied CE mark. This means that these devices have been sold without evidence of safety and have been manufactured to unknown standards. Stop using these devices and use a suitable alternative. Actions for the Patient Safety Lead in healthcare Institutions 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.

Article citation: Drug Safety Update volume 15, issue 8: March 2022: 5.