Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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In our first article, we remind healthcare professionals that elderly patients are at an increased risk of adverse neurological and cardiac effects when being treated with haloperidol for delirium. The lowest possible dose of haloperidol should be used for the shortest possible time, and cardiac and extrapyramidal adverse effects should be closely monitored.

In our second article, we include updated measures aiming to reduce the risk of tumour lysis syndrome (TLS) in all patients treated with venetoclax, indicated for chronic lymphocytic leukaemia and acute myeloid leukaemia. Fatal cases of TLS have been reported, some occurring in patients with chronic lymphocytic leukaemia receiving the lowest venetoclax dose used in the dose-titration schedule.

In our third article, we inform prescribers that the authorisation holder for dapagliflozin has withdrawn the indication for type 1 diabetes mellitus. Discontinuation of dapagliflozin should be done by or under the care of a diabetes specialist and requires frequent blood glucose monitoring.

On page 13 we summarise recent advice relating to COVID-19 vaccines and medicines published since the November 2021 issue of Drug Safety Update. And on page 15 we include recent letters, recalls and notifications sent to healthcare professionals about medicines.

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Haloperidol (Haldol): reminder of risks when used in elderly patients for the acute treatment of delirium

We remind healthcare professionals that elderly patients are at an increased risk of adverse neurological and cardiac effects when being treated with haloperidol for delirium. The lowest possible dose of haloperidol should be used for the shortest possible time, and cardiac and extrapyramidal adverse effects should be closely monitored.

Advice for healthcare professionals:

- special caution is required when using haloperidol for the acute treatment of delirium in frail, elderly patients
- only consider haloperidol for delirium when non-pharmacological interventions are ineffective and no contraindications are present (including Parkinson's disease and dementia with Lewy bodies)
- before initiating treatment, a baseline electrocardiogram (ECG) and correction of any electrolyte disturbances is recommended; cardiac and electrolyte monitoring should be repeated during treatment (see below)
- prescribe the lowest possible dose for the shortest possible time, ensuring that any dose up-titration is gradual and reviewed frequently
- monitor for and investigate early any extrapyramidal adverse effects, such as acute dystonia, parkinsonism, tardive dyskinesia, akathisia, hypersalivation, and dysphagia
- report suspected adverse reactions associated with haloperidol on a Yellow Card

Review of haloperidol use in elderly patients with delirium

Haloperidol is a first-generation antipsychotic authorised for treatment of neurological and psychiatric disorders, including the acute treatment of delirium in adults when non-pharmacological treatments have failed – see the Summary of Product Characteristics (SmPC) for full indications.

The MHRA received concerns from a patient representative regarding the use of haloperidol for the acute treatment of delirium in elderly people in the UK. The MHRA conducted a review of UK safety information for haloperidol in the treatment of delirium in frail, elderly patients. The review included safety data from the Yellow Card scheme as well the published literature and current clinical guidance. We sought advice on the review assessment from the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines and experts in neurology and psychiatry. We have made available a Public Assessment Report.

The review did not identify any new safety concerns relating to use of haloperidol in elderly patients and no changes will be made to the safety advice in the product information. However, the review identified that the practical use of haloperidol in patients with delirium is variable and is known to be especially associated with adverse effects of the central nervous system.

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We issue this reminder to healthcare professionals, especially prescribers of haloperidol, to emphasise the need for special caution when using this medicine in elderly people. This advice is consistent with current clinical advice for management of delirium in this population.

Clinical advice available on treatment of delirium

Delirium or ‘acute confusional state’ is a common and complex condition that is known to occur more frequently in older people. Diagnosis and treatment of newly presenting delirium in elderly people can be challenging as it is often multifactorial.

Clinical guidance recommends that patients are reviewed, and screening tools used. Delirium may also overlap with dementia or other precipitating factors such as polypharmacy or infection, which can be especially relevant in elderly patients. Frailty (defined by NHS England as ‘a loss of resilience that means people don't bounce back quickly after a physical or mental illness, an accident or other stressful event’) can further increase the risk.

Clinical guidance recommends that pharmacological interventions for acute treatment of delirium are kept to a minimum with non-pharmacological interventions used first-line. However, in cases of delirium where these methods have failed and the patient is distressed or there is a risk to their safety or those around them, then clinical guidance recommends low-dose, short-term haloperidol unless contraindicated.

Full contraindications can be found in the Summary of Product Characteristics (SmPC). Haloperidol is contraindicated in patients with Parkinson's disease and dementia with Lewy bodies. Relevant clinical guidance should be consulted for care of these patients.

Clinical guidance, especially on dosing and monitoring for patients with delirium, should be referred to such as NICE guidance on delirium, SIGN guidance risk reduction and management of delirium, and British Geriatrics Society guidance on patients presenting with confusion and delirium. During the coronavirus (COVID-19) pandemic, haloperidol has also been used for the treatment of delirium associated with COVID-19.

Reminder of dosing recommendations in elderly patients

Elderly patients may have a lower clearance and longer elimination half-life of haloperidol. Dose adjustment is therefore recommended for patients with hepatic or renal impairment, as well as patients who are elderly. Prescribers should refer to local and national prescribing guidelines, as well as the dosing principles in the SmPC.

First dosing should always be very cautious, especially in elderly people, and the minimum effective dose should be prescribed for the shortest possible time. Any dose up-titration should be gradual and reviewed frequently. Regular reviews should be conducted, with the aim of discontinuing haloperidol treatment as soon as is feasible.

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Reminder of neurological and cardiac side effects of haloperidol

Since 1964 and up to 4 September 2021, the MHRA had received a total of 1341 Yellow Card reports containing 3385 suspected adverse drug reactions relating to haloperidol. Of these, 242 reports related to patients from 60 years of age or older and the majority of the reactions (171) related to adverse effects in the nervous system.[1]

Elderly patients may be particularly susceptible to extrapyramidal side effects with haloperidol. These can be potentially serious and should be carefully monitored and promptly investigated. Extrapyramidal side effects may include acute dystonias, parkinsonism, or tardive dyskinesia, each of which may impair a patient's ability to swallow, a complication of which can be inhalation of throat or stomach contents and eventually aspiration pneumonia. Healthcare professionals are encouraged to undertake early monitoring and investigation of drug-induced dysphagia in elderly patients.

Haloperidol is also associated with QTc prolongation and ventricular arrhythmias. Accordingly, use of haloperidol is contraindicated in patients with known QTc prolongation, congenital long QTc syndrome and in patients taking other drugs known to prolong the QTc interval – examples are provided in the Interactions section of the SmPC.

A baseline ECG is recommended before treatment, particularly in patients with cardiovascular risk factors or a history of cardiovascular disease. The need for further ECGs during treatment should be assessed on an individual basis, and blood pressure monitoring during treatment is also advised.

Dose-related orthostatic hypotension is known to occur in elderly people treated with haloperidol, which may increase the risk of falls.

Other adverse reactions listed in the product information include rhabdomyolysis and rare cases of neuroleptic malignant syndrome, for which prompt medical intervention is required

Clinical evidence base for use of haloperidol in delirium

The review identified that there are limited randomised controlled trials of haloperidol for the treatment of delirium, particularly in elderly patients, an issue contributed to by the practical and ethical difficulties associated with studies of this kind. However, haloperidol has been used extensively worldwide for many years.

Current clinical guidelines on delirium rely on expert opinion in this area of antipsychotic prescribing. Further study of the behavioural disturbances associated with delirium in elderly patients is needed and current clinical guidelines include recommendations for more research.

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Report suspected adverse drug reactions

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.

Footnotes:

1. In interpreting these data, caution should be exercised as data may not be complete, and the reporting rates can be influenced by many factors. Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine may have caused the adverse drug reaction.

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Venetoclax (Venclyxto▼): updated recommendations on tumour lysis syndrome (TLS)

Fatal cases of tumour lysis syndrome (TLS) have been reported, some occurring in patients with chronic lymphocytic leukaemia receiving the lowest venetoclax dose used in the dose-titration schedule. For all patients, it is important to strictly adhere to the dose-titration schedule and to the measures to minimise the risk of TLS as outlined in the updated Summary of Product Characteristics (SmPC).

Advice for healthcare professionals:

- tumour lysis syndrome (TLS) is a known risk of venetoclax; fatal cases have been reported, with some occurring in patients with chronic lymphocytic leukaemia receiving a single dose of venetoclax 20 milligrams (the lowest dose used in the dose-titration phase) and in patients with low-to-medium TLS risk
- for all patients prescribed venetoclax, perform TLS risk assessment and adhere to guidance on appropriate prophylactic measures (including hydration and anti-hyperuricaemics), laboratory monitoring (including blood chemistries), dose titration, and drug interactions
- refer to appropriate sections of the SmPC for the full specific advice on prevention and management of TLS during treatment with venetoclax for each indication (chronic lymphocytic leukaemia and for acute myeloid leukaemia)
- advise patients about TLS and measures to reduce the risk, discuss the symptoms of TLS, and provide the Patient Information Leaflet and the patient card (for patients with chronic lymphocytic leukaemia)
- report any suspected adverse drug reactions associated with black triangle medicines to the Yellow Card scheme

Advice for healthcare professionals to provide to patients:

- venetoclax treatment is associated with tumour lysis syndrome (TLS), a complication that occurs when the cancer cells are destroyed too quickly and release unusual levels of some body salts (such as uric acid and potassium) into the blood
- the risk for TLS occurs in the first days or weeks of treatment with venetoclax, as your dose is increased
- follow your doctor's instructions on drinking plenty of water, having frequent blood tests, and taking medicines to prevent the build-up of uric acid
- if you are taking venetoclax for chronic lymphocytic leukaemia, your doctor will give you the patient card; carry this card with you at all times and share it with healthcare professionals involved in your care
- TLS can be very serious if untreated; if you develop any of the TLS symptoms listed in the Patient information Leaflet, stop taking your tablets and talk to a healthcare professional immediately
- always read the Patient Information Leaflet that accompanies your medicines and talk to your healthcare professionals if you are concerned

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Risk of tumour lysis syndrome with venetoclax

Venetoclax is a B-cell lymphoma-2 (BCL-2) inhibitor authorised in the UK for the treatment of chronic lymphocytic leukaemia and more recently for acute myeloid leukaemia (see section on details of full authorisation for full indications).

Tumour lysis syndrome (TLS) is a known important risk with venetoclax treatment. Cases have been reported in clinical trials and in clinical use (post-marketing), including in the UK (see section on Frequency information).

TLS has been associated with severe consequences including renal failure requiring dialysis and death. Risk minimisation measures should be followed to reduce the risk of TLS. If TLS is suspected, urgent medical attention is required. The risk of TLS is a continuum based on multiple factors, including comorbidities (particularly reduced renal function) and tumour burden, and splenomegaly (in chronic lymphocytic leukaemia).

Information about the risk of TLS has been present in the SmPC and Patient Information Leaflet for venetoclax since authorisation, but precautions were previously focused on risk factors such as level of tumour burden.

Characteristics of TLS

The administration of venetoclax can cause rapid reduction in tumour burden. Thus, the risk for TLS is present at treatment initiation and during the dose-titration phase.

TLS may lead to blood chemistry changes (hyperuricaemia, hyperkalaemia, hyperphosphataemia, and hypocalcaemia), which can sometimes progress to clinically toxic effects, including renal insufficiency, cardiac arrhythmias, seizures, and death (so-called clinical TLS).

Changes in electrolytes consistent with TLS requiring prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and also at each dose increase. Blood chemistries should be monitored and abnormalities managed promptly.

Patients should stop taking their tablets and seek medical attention immediately if they have any of the signs and symptoms of TLS listed in the Patient Information Leaflet.

Review of TLS risk with venetoclax

Fatal cases of TLS have been reported in the post-marketing setting in patients with chronic lymphocytic leukaemia treated with venetoclax. Some of these events have occurred in patients receiving a single dose of venetoclax 20 milligrams (the lowest dose used at initiation and during the dose-titration phase) and in patients with low-to-medium TLS risk.

Following a European safety data assessment, including these fatal cases, the SmPC warnings were updated to include that fatal events of TLS have been reported after a single 20mg dose. Information in the Special warnings and precautions section of the SmPC has been revised to emphasise that all patients should be assessed for the risk of TLS, and that treatment with venetoclax requires adequate risk assessment that considers comorbidities (particularly reduced renal function) and other risk factors such as splenomegaly (in chronic lymphocytic leukaemia).

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All patients should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricaemics. New tables have been added in the posology section of the SmPC to clarify TLS risk minimisation based on the level of tumour burden and display recommended dose modifications for toxicities.

A letter to prescribers was sent in June 2021 to communicate the new advice. Since then, a patient card has also been sent to healthcare professionals to provide to each patient with chronic lymphocytic leukaemia undergoing venetoclax treatment. These patients should be advised to carry the card with them at all times and provide the card to any healthcare professional they see for information.

Cases of TLS associated with venetoclax treatment for acute myeloid leukaemia have been reported. The SmPC provides specific advice to prevent and reduce the risk of TLS during treatment with venetoclax in patients with acute myeloid leukaemia.

Frequency of TLS during venetoclax treatment

In the SmPC the frequency of TLS in patients with chronic lymphocytic leukaemia treated with venetoclax is listed as common (may affect up to 1 in 10 people), both at any grade and for grade 3 or higher reactions. This is based on clinical trial data. Similarly, the frequency of TLS in patients with acute myeloid leukaemia treated with venetoclax is listed as common, with grade 3 or higher reactions listed as uncommon (may affect up to 1 in 100 people).

Since authorisation and up to 6 October 2021, we have received 28 Yellow Card reports where TLS was reported as a suspected adverse drug reaction (ADR) in association with venetoclax treatment. Where indication was reported, 12 reports were associated with use of venetoclax in chronic lymphocytic leukaemia and 6 with use in acute myeloid leukaemia.[1] Of the 28 reports, there were 7 deaths. We are aware of a report of TLS and fatal cardiac arrest in a patient with chronic lymphocytic leukaemia in which the reporter noted that the venetoclax drug dose-titration was not performed.

Details of the full authorisation for venetoclax

Venetoclax is currently authorised in the UK:

- in combination with obinutuzumab, for adults with previously untreated chronic lymphocytic leukaemia
- in combination with rituximab, for adults with chronic lymphocytic leukaemia who have received at least one prior therapy
- as monotherapy, for the treatment of chronic lymphocytic leukaemia
    - in the presence of 17p deletion or *TP53* mutation in adults who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
    - in the absence of 17p deletion or *TP53* mutation in adults who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.
- in combination with a hypomethylating agent, for adults with newly diagnosed acute myeloid leukaemia who are ineligible for intensive chemotherapy

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Report on a Yellow Card

Venetoclax ▼ is under additional monitoring and any suspected adverse drug reactions (ADRs) should be reported to the MHRA via 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 medical history, any concomitant medication, onset timing, treatment dates, and product brand name.

Report suspected side effects to medicines, vaccines or 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.

Footnotes:

1. In interpreting these data, caution should be exercised as data may not be complete, and the reporting rates can be influenced by many factors. Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine may have caused the adverse drug reaction.

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Dapagliflozin (Forxiga): no longer authorised for treatment of type 1 diabetes mellitus

The authorisation holder for dapagliflozin has withdrawn the indication for type 1 diabetes mellitus. The removal of the type 1 diabetes indication is not due to any new safety concerns and the other indications of dapagliflozin are unchanged.

Advice for healthcare professionals:

- dapagliflozin 5 mg is no longer authorised for the treatment of patients with type 1 diabetes mellitus
- the removal of the type 1 diabetes indication is not due to any new safety concerns and the other indications of dapagliflozin are unchanged
- dapagliflozin should be reviewed and discontinued in patients with type 1 diabetes by or in consultation with a physician specialised in diabetes care as soon as clinically practical
- after stopping dapagliflozin treatment, frequent blood glucose monitoring is recommended
- an increased insulin dose may be needed, which should be undertaken carefully to minimise the risk of hypoglycaemia or hyperglycaemia
- diabetic ketoacidosis is a known risk with use of dapagliflozin in all patients with diabetes, but it occurs more frequently in patients with type 1 diabetes than those with type 2 diabetes
- additional risk minimisation materials to mitigate the risks in patients with type 1 diabetes are no longer available
- report suspected adverse drug reactions associated with use of dapagliflozin on a Yellow Card

Advice for healthcare professionals to provide to patients and carers:

- always seek advice from your doctor or diabetes team before making changes to your diabetes medicines
- the manufacturer of dapagliflozin (Forxiga) has voluntarily withdrawn its use in type 1 diabetes
- this decision was not linked to a new safety issue and other patients using dapagliflozin for type 2 diabetes, heart failure, or chronic kidney disease can continue taking their medicine as recommended by a healthcare professional
- if you take dapagliflozin for your type 1 diabetes, your specialist will help you safely discontinue this treatment – you will need to monitor your blood glucose levels more closely to prevent hypoglycaemia or hyperglycaemia in the transition

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Dapagliflozin indications

For the full indications see the Summary of Product Characteristics (SmPC).

Sodium glucose co-transporter 2 (SGLT2) inhibitors act to improve glycaemic control by reducing glucose reabsorption and increasing urinary glucose excretion. The SGLT2 inhibitor dapagliflozin has been indicated for the treatment of type 2 diabetes since 2012 and is also indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction and for the treatment of chronic kidney disease.

Dapagliflozin (Forxiga) was authorised in 2019 as an adjunct to insulin in patients with type 1 diabetes with a body-mass index (BMI) of 27 kg per m^2 or higher, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

Withdrawal of type 1 diabetes indication

On 25 October 2021, the marketing authorisation holder for dapagliflozin withdrew the indication for type 1 diabetes across Europe and in the UK. A letter was sent to UK healthcare professionals to inform them of the withdrawal. As such, patients with type 1 diabetes should discontinue dapagliflozin 5mg in consultation with their specialist diabetes physician as soon as clinically practical.

Dapagliflozin has a diuretic effect and has been associated with a decrease in blood pressure. It should therefore be noted that a small increase in blood pressure may be seen upon discontinuation of dapagliflozin.

Dapagliflozin was the only SGLT2 inhibitor that was available for treatment of type 1 diabetes. The use of dapagliflozin 5mg for the treatment of type 1 diabetes required specific additional risk minimisation measures for the risk of diabetic ketoacidosis, including a patient alert card and a healthcare professional guide. This reflected the increased risk in type 1 compared with type 2 diabetes, with studies in type 1 diabetes reporting diabetic ketoacidosis with a common frequency (may affect up to 1 in 10 patients), and cases reported of euglycaemic diabetic ketoacidosis. As a result of the indication removal, the additional risk minimisation materials are no longer available.

The decision by the marketing authorisation holder to voluntarily withdraw the indication in type 1 diabetes followed commercial considerations due to a specific European-wide regulatory requirement for this authorisation. The decision was not driven by any new safety concerns, such as the already known increased risk of diabetic ketoacidosis in type 1 diabetes compared with type 2 diabetes.

Other indications for dapagliflozin 5mg and 10mg are not affected by this licensing change and both strengths will remain on the market. Dapagliflozin remains authorised in adults for the treatment of type 2 diabetes, for the treatment of symptomatic chronic heart failure with reduced ejection fraction, and for the treatment of chronic kidney disease.

Guidance should be consulted on prescribers' responsibilities if using a medicine off-label or using an unlicensed medicine. For any use of SGLT2 inhibitors, follow advice on the risk of diabetic ketoacidosis in the product information, and consult past Drug Safety Update advice on minimising the risk of diabetic ketoacidosis with use of SGLT2 inhibitors in type 2 diabetes and monitoring ketones during treatment interruption due to surgery or acute illness.

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Report suspected reactions on a Yellow Card

Suspected adverse drug reactions associated with dapagliflozin should be reported 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.

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COVID-19 vaccines and medicines: updates for December 2021

Recent information relating to COVID-19 vaccines and medicines that has been published since the November 2021 issue of Drug Safety Update, up to 3 December 2021.

Approval of Xevudy (sotrovimab), a monoclonal antibody treatment for COVID-19

We have approved Xevudy (sotrovimab) following a rigorous review of its safety, quality and effectiveness by us and the government's independent expert scientific advisory body, the Commission on Human Medicines (CHM). This is the second monoclonal antibody therapeutic to be approved following Ronapreve.

Xevudy (sotrovimab) is safe and effective at reducing the risk of hospitalisation and death in people with mild to moderate COVID-19 infection who are at an increased risk of developing severe disease.

Xevudy works by interfering with the replication of the virus, binding to the COVID-19 spike protein and preventing the virus from attaching to and entering human cells. Based on the clinical trial data, sotrovimab is most effective when taken during the early stages of infection and so the MHRA recommends its use as soon as possible and within five days of symptom onset.

Like the antiviral molnupiravir, Xevudy has been authorised for use in people who have mild to moderate COVID-19 infection and at least one risk factor for developing severe illness. Such risk factors include obesity, older age (over 55 years), diabetes mellitus, or heart disease. Unlike molnupiravir, sotrovimab is administered by intravenous infusion over 30 minutes. It is approved for individuals aged 12 and above who weigh more than 40kg.

For more information about Xevudy (sotrovimab), see our Press release and Decision page which includes the Summary of Product Characteristics and Patient Information Leaflet.

Summaries of Yellow Card reporting and other recent MHRA publications

See guidance on COVID-19 for all our latest information, including after publication of this article.

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 sections of the Summary of Product Characteristics and Patient Information Leaflet for COVID-19 Vaccine Pfizer/BioNTech to include information about receiving a third/booster dose, added the official international non-proprietary name 'tozinameran' and included two new reagents, sodium hydroxide and hydrochloric acid, which are used in small quantities during the preparation of one of the solutions used in the manufacturing process
- published the Public Assessment Report (PAR) for Ronapreve, an antibody treatment for COVID-19. Please see the Decision page on our website which has more details about Ronapreve
- published a statement on the expansion of the COVID-19 vaccination booster programme

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We previously included summaries of latest COVID-19 information, including in the August 2021, September 2021 and November 2021 issues of Drug Safety Update.

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 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 timing, treatment dates, and vaccine product brand name and batch number.

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

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Letters and medicine recalls sent to healthcare professionals in November 2021

Letters

In November 2021, the following letters were sent or provided to relevant healthcare professionals:

- Beovu ▼ (brolucizumab): updated recommendations to minimise the known risk of intraocular inflammation, including retinal vasculitis and/or retinal vascular occlusion
- Forxiga (dapagliflozin) 5mg should no longer be used for the treatment of Type 1 Diabetes Mellitus (see accompanying article on page 10)
- Mitocin (mitomycin) 20mg powder for solution for injection/infusion or intravesical use: new single-use filtration device must be used to avoid patient exposure to subvisible particles and reduce risk of injection reactions
- Zavedos (idarubicin) 5mg and 10mg Powder for Solution for Injection: Temporary supply of unlicensed 5mg/5ml and 10mg/10ml presentations to UK market; important differences in storage, preparation and administration
- Fluad Tetra (Influenza vaccine (surface antigen, inactivated, adjuvanted)) 0.5ml 10x1 PFS: Interim Supply to Great Britain to Mitigate Supply Disruption

Medicine Recalls and Notifications

In November 2021, recalls and notifications for medicines were issued on:

UPDATE: Class 4 Medicines Defect Information: Crescent Pharma Ltd, SyreniRing 0.120 mg/0.015 mg per 24 hours, vaginal delivery system, EL (20)A/36. Issued 2 November 2021. Additional batches of SyreniRing 0.120 mg/0.015 mg (etonogestrel and ethinylestradiol) have been identified to contain Patient Information Leaflets missing important safety relevant text changes. An updated batch list has been included on the original defect notification issued in August 2020. Healthcare professionals dispensing this product should ensure patients are aware of any missing information.

Class 4 Medicines Defect Information: Vygoris Limited, Mitocin (mitomycin) 20mg powder for solution for injection/infusion or intravesical use, EL (21)A/27. Issued 8 November 2021. Some vials of Mitocin 20mg (mitomycin) powder for solution for injection/infusion or intravesical use may contain subvisible particles above the current specifications after reconstitution. The manufacturer will include a single-use filtration device with all future stock of Mitocin 20mg and healthcare professionals may request additional filters from the manufacturer. Healthcare professionals are advised to check existing stock and ensure that prior to treatment, the single-use filters are used.

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Class 2 Medicines Recall: Cold & Flu Relief Capsules (GSL) – Various Liveries, Wrafton Laboratories Limited (trading as Perrigo), EL (21)A/28. Issued 11 November 2021. Batches of Cold and Flu relief capsules (Paracetamol 300 mg, Caffeine 25 mg and Phenylephrine hydrochloride 5 mg) in various liveries are being recalled due to an error on the product carton and leaflet. The affected products incorrectly state the posology for individuals over 12 years as 2 capsules every 4 to 6 hours as required, up to a maximum of 12 capsules in any 24-hour period. This exceeds the paediatric paracetamol limits for children aged 12–15 years where the correct posology is up to a maximum of 8 capsules in any 24-hour period. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 4 Medicines Defect Information: Slenyto 1 mg and 5mg prolonged-release tablets – distributed by Flynn Pharma Ltd, EL (21)A/29. Issued 15 November 2021. Batches of Slenyto 1mg and 5mg (melatonin) prolonged-release tablets have been identified to be missing important safety relevant text from the Patient Information Leaflets. The Patient Information Leaflets in affected batches do not contain the interaction with beta-blockers or details of pack sizes. Healthcare professionals are advised to exercise caution when dispensing the product and where possible provide an updated Patient Information Leaflet to patients.

Company led medicines recall: Dotarem solution for injection (10ml Vial) - PL 12308/0016. Issued 17 November 2021. Batches of Dotarem (gadoteric acid) solution for injection 10ml vials are being recalled due to defects in the glass vial neck leading to leakage and potential loss of sterility. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 2 Medicines Recall: SANTEN Oy (trading as Santen UK Limited) and parallel distributor, IKERVIS 1 mg/mL eye drops, emulsion and VERKAZIA 1 mg/mL eye drops, emulsion, EL (21)A/30. Issued 18 November 2021. Batches of Ikervis 1mg/ml eye drops and Verkazia 1mg/mL eye drops (ciclosporin) are being recalled due to particles or crystals of the active ingredient detected during stability testing. No reports of adverse events have been received by the Marketing Authorisation Holder, but there is potential for ocular irritation, eye pain or foreign body sensation due to the presence of particles. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 3 Medicines Recall: Martindale Pharma, an Ethypharm Group Company Methadone 5mg Tablets / Physeptone 5mg Tablets, EL (21)A/31. Issued 22 November 2021. A batch of methadone 5mg tablets is being recalled as a precaution due to discolouration of the blister pockets film. Stop supplying the batch immediately, quarantine all remaining stock and return to supplier.

Class 4 Medicines Defect Information: Diuril Oral Solution (unlicensed medicine), Mawdsley-Brooks & Company Limited, EL (21)A/32. Issued 29 November 2021. Batches of Diuril (chlorothiazide) oral solution have been identified with incorrect product information. The Patient Information Leaflet in affected batches states an incorrect alcohol content of 0.4%, whilst the bottle, carton and Patient Information Leaflet inside the pack correctly state 0.5% alcohol content. Healthcare professionals are advised to use caution when dispensing the product and use the manufacturers Patient Information Leaflet inserted in the pack.

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Class 4 Medicines Defect Information: Mometasone Furoate 50 Microgram / Dose Nasal Spray, Suspension, PilsCo Ltd, EL (21)A/33. Issued 29 November 2021. Batches of mometasone furoate 50 microgram nasal spray have been identified with incorrect usage instructions. Affected batches contain a bottle label that incorrectly advises the product should be used within 2 weeks of first use, as the correct statement is to use within 2 months of first use. The correct wording is present in the Patient Information Leaflet and on the product carton. Healthcare professionals are advised to exercise caution when dispensing the product and instruct the patient to ensure they use the product within 2 months of first use.

Class 2 Medicines Recall: Various Marketing Authorisation Holders and parallel distributor companies, Irbesartan-containing products, EL(21)A/34. Issued 30 November 2021. Batches of the following medicines are being recalled by multiple manufacturers and distributors: Aprovel (irbesartan) 150mg and 300mg film-coated tablets, Co-Aprovel (irbesartan and hydrochlorothiazide) 150mg/12.5mg, 300mg/12.5mg Film-Coated Tablets. This is a precautionary recall as batches have been identified to contain 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2yl)-1H-tetrazole, an impurity of mutagenic potential that is above the acceptable limits. Stop supplying the batches immediately, quarantine all remaining stock and return to supplier. Healthcare professionals should advise patients not to stop taking their medicine without consulting their doctor or pharmacist. The MHRA will provide further updates as our investigation progresses.

See Alerts, recalls and safety information for all recent notices.

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