

Drug Safety Update



MHRA

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

Volume 13 Issue 1 August 2019

Contents

Daratumumab (Darzalex ▼): risk of reactivation of hepatitis B virus	page 2
Naltrexone/bupropion (Mysimba ▼): risk of adverse reactions that could affect ability to drive	page 4
Carfilzomib (Kyprolis ▼): reminder of risk of potentially fatal cardiac events	page 6
Letters and drug alerts sent to healthcare professionals in July 2019	page 8
Medical Devices Alerts issued in July 2019	page 9

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.



MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal:
www.evidence.nhs.uk/

To subscribe to monthly email alerts of Drug Safety Update see:
<https://www.gov.uk/drug-safety-update>

First, we inform of worldwide cases of hepatitis B virus reactivation, some fatal, in patients receiving daratumumab for multiple myeloma (page 2). Hepatitis B virus status should be established before initiating daratumumab and should also be confirmed in patients with unknown serology who are already being treated with daratumumab.

On page 4, we ask prescribers and dispensers of naltrexone/bupropion (Mysimba ▼), indicated for weight management in patients with obesity, to discuss with patients the risk of adverse reactions such as dizziness and somnolence, which can affect ability to drive, operate machinery, or perform dangerous tasks. We reiterate the importance of healthcare professionals advising patients to read the patient information leaflet accompanying medicines for information about possible side effects that may impair driving.

On page 6, we remind healthcare professionals that anti-cancer therapy with carfilzomib has been associated with cardiac events such as cardiac failure and myocardial infarction, including in patients without pre-existing cardiac disorders.

Finally see our highlight of recent letters and alerts on pages 8 and 9, including recall of medicines taken out of the regulated medicines' supply chain during distribution. A patient-level recall of relevant batches of Neupro 4 mg/24hr patches and Vimpat 100mg tablets is ongoing.

drugsafetyupdate@mhra.gov.uk

Daratumumab (Darzalex ▼): risk of reactivation of hepatitis B virus

Establish hepatitis B virus status before initiating daratumumab and in patients with unknown hepatitis B virus serology who are already being treated with daratumumab.

Advice for healthcare professionals:

- hepatitis B virus reactivation has been reported in patients treated with daratumumab, including several fatal cases worldwide
- screen all patients for hepatitis B virus before initiation of daratumumab; patients with unknown serology who are already on treatment should also be screened
- monitor patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during treatment, and for at least 6 months following the end of daratumumab treatment
- advise patients with positive serology to seek medical help immediately if they experience signs and symptoms suggestive of hepatitis B virus reactivation
- stop treatment with daratumumab in patients with hepatitis B virus reactivation and institute appropriate treatment in consultation with experts in the treatment of hepatitis B virus infection; consult with experts before resuming daratumumab in patients with adequately controlled viral reactivation
- report any suspected adverse drug reactions associated with daratumumab to the [Yellow Card Scheme](#)

Review of cases of hepatitis B reactivation

A recent EU cumulative review of worldwide data has identified reports of hepatitis B virus reactivation in patients treated with daratumumab.

There have been 6 cases of hepatitis B virus reactivation observed in clinical trials in patients with multiple myeloma. Most of these cases were considered non-serious, although fatal hepatitis B virus reactivation cases have been reported in clinical trials. There have also been reports from the post-marketing setting. Nearly all cases have been observed in the first 6 months of daratumumab treatment. In some cases, daratumumab has been reinitiated once hepatitis B virus reactivation has been controlled with antiviral medication.

No cases of hepatitis B virus reactivation associated with daratumumab have been reported in the UK via the Yellow Card Scheme. Nevertheless, prescribers should be vigilant for the risk in UK patients and ensure serology is established in all patients being treated with daratumumab.

Risk factors of hepatitis B reactivation

In patients on daratumumab who have had hepatitis B virus reactivation, risk factors included:

- previous autologous stem cell transplant (ASCT)
- concurrent and/or prior lines of immunosuppressive therapy

Residence in or immigration from regions of high hepatitis B prevalence may also present a higher risk of hepatitis B seropositivity.

Identification of the role of daratumumab therapy in the reported cases of hepatitis B virus reactivation is complicated by the underlying medical condition, given that patients with multiple myeloma are immunosuppressed. In several cases, patients were also receiving concomitant medications associated with viral reactivation. However, because a causal relationship cannot be ruled out, the product information for daratumumab will be updated to reflect the new safety information

[Letter sent to healthcare professionals.](#)

[Darzalex Summary of Product Characteristics](#)

Background

[Daratumumab](#) is indicated:

- in combination with bortezomib, melphalan, and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

Report any suspected adverse drug reactions

Daratumumab ▼ is subject to additional monitoring and any suspected adverse drug reactions (ADR) should be reported to the Yellow Card Scheme.

Report on the [Yellow Card website](#) or via the Yellow Card app (download via [iTunes Yellow Card](#) for iOS devices or via [PlayStore Yellow Card](#) for Android devices).

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 1: August 2019: 1.

Naltrexone/bupropion (Mysimba ▼): risk of adverse reactions that could affect ability to drive

Advise patients that naltrexone/bupropion has been associated with adverse reactions such as dizziness or somnolence, which can affect ability to drive, operate machinery, or perform dangerous tasks. Advise patients not to drive if they suspect their ability may be impaired.

Advice for healthcare professionals:

- people taking naltrexone/bupropion may commonly experience dizziness or somnolence, and may rarely experience loss of consciousness or seizure
- these effects would pose a risk to their ability to drive or operate machinery especially at the beginning of the treatment or during the dose titration phase
- advise patients experiencing adverse reactions with naltrexone/bupropion to not drive or operate machinery until they have resolved

Advice for healthcare professionals to give to patients about any medicine that may impair driving:

- always check the leaflet that comes with your medicine for information on how your medicine may affect your driving ability
- it is against the law to drive if your driving ability is impaired by any medicine
- do not drive if you have side effects that may impair driving, such as difficulties with vision or concentration; feeling sleepy, dizzy, or faint; or seizures (fits)
- do not drive, operate machinery, or perform dangerous activities while taking a medicine until you know how it affects you (especially just after starting or changing the dose of the medicine)
- talk to your doctor or pharmacist if you have concerns about side effects while taking a medicine; side effects can be reported to the [Yellow Card Scheme](#)

Enhanced driving warning

[Mysimba Summary of Product Characteristics](#)

Naltrexone/bupropion ([Mysimba ▼](#)) is authorised in conjunction with diet and exercise for the management of weight in obese adults and in overweight adults with 1 or more weight-related conditions. At the time of publication, use of Mysimba in the UK is low and it is normally available only on private prescription.

An EU review of cumulative data has identified somnolence as a common risk with naltrexone/bupropion and loss of consciousness as a rare risk. Given these and other adverse reactions, a new warning has been added to the product information that naltrexone/bupropion may affect the ability to drive, operate machinery, or perform dangerous tasks.

In a few cases, loss of consciousness occurred when the patient was driving, including a small number of cases worldwide associated with a road traffic accident. As of publication of this article, no adverse drug reaction reports for naltrexone/bupropion received through the UK Yellow Card Scheme have indicated a road traffic accident was associated with the reported event.

Patients should be advised not to drive, operate machinery, or perform dangerous activities while taking naltrexone/bupropion until they know how the medicine affects them. This should be considered especially just after starting or changing the dose of the medicine.

Reminder: medicines and driving

It is against the law for a person in the UK to drive if their driving ability is impaired by any medicine. Please continue to discuss with patients any potential driving impairment associated with medicines you have prescribed and dispensed. The advice provided about driving in the Patient Information Leaflet for all medicines can form the basis for this discussion. Advice for healthcare professionals about the influence of a medicine on driving ability is also provided in section 4.7 of the Summary of Product Characteristics for all medicines.

Healthcare professionals may wish to consult the [DVLA's guidance for assessing a patient's fitness to drive](#), if the patient experiences an adverse reaction that may affect their driving ability, for example if a recent loss of consciousness or seizure is suspected.

In England and Wales, it is also illegal to drive with blood concentrations of certain controlled drugs above pre-specified limits. See [Drug Safety Update from 2015](#) for more information.

Report suspected adverse drug reactions via the Yellow Card Scheme

Please continue to report any suspected adverse drug reaction via the [Yellow Card Scheme](#). Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card.

Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website or via the Yellow Card app. Download the app today via [iTunes Yellow Card](#) for iOS devices or via [PlayStore Yellow Card](#) for Android devices.

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

Article citation: Drug Safety Update volume 13, issue 1: August 2019: 2.

Carfilzomib (Kyprolis ▼): reminder of risk of potentially fatal cardiac events

Anti-cancer therapy with carfilzomib has been associated with cases of cardiac arrest, cardiac failure, and myocardial infarction, including in patients without pre-existing cardiac disorders. Monitor patients for signs and symptoms of cardiac disorders before and during exposure to carfilzomib.

Advice for healthcare professionals:

- cases of cardiac arrest, cardiac failure, and myocardial infarction, including fatal cases, have been reported in patients receiving anti-cancer therapy with carfilzomib – not all cases occurred in patients with a pre-existing cardiac disorder
- monitor patients for signs and symptoms of cardiac disorders before and during treatment with carfilzomib
- stop carfilzomib if severe or life-threatening cardiac events occur; restarting treatment may be considered at a lower dose once the condition is controlled and the patient is functionally stable
- report any suspected adverse drug reactions (ADR) associated with carfilzomib via the [Yellow Card Scheme](#)

Reminder of risk of cardiac events with carfilzomib

Carfilzomib is indicated in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.

[Kyprolis
Summary of
Product
Characteristics](#)

Carfilzomib has been associated with new or worsening cardiac failure, decreased ejection fraction, pericarditis, atrial fibrillation, tachycardia, myocardial ischaemia, and myocardial infarction – see section 4.4 of the [Summary of Product Characteristics](#). Death due to cardiac arrest has occurred within a day of carfilzomib administration and fatal outcomes have also been reported following cardiac failure and myocardial infarction.

MHRA recently received a report from a Coroner following death by cardiac arrest of a man given carfilzomib, cyclophosphamide, and dexamethasone in a clinical trial. The [Pharmacovigilance Expert Advisory Committee](#) of the Commission on Human Medicines considered the safety profile for carfilzomib and risks of cardiac reactions. The Committee advised that warnings about risks in the product information of carfilzomib are clear but emphasised the need for prescribers to be reminded of the risk.

Data derived from IQVIA MIDAS, 01/2018-12/2018, and analysed by the MHRA, May 2019

UK suspected adverse drug reactions

In 2018, approximately 22,000 vials of carfilzomib were dispensed in the UK, making the estimated UK exposure since launch about 84,000 vials.¹

Since 2013 and up to July 2019, 5 cases of cardiac failure, 5 of arrhythmia, 3 of cardiac arrest, 2 of pericarditis, 2 of left ventricular failure, and 5 of myocardial infarction, of which 6 were fatal (including the Coroner's case), have been reported in the UK in post-

marketing settings and in clinical trials in patients administered carfilzomib. Some of the patients in these cases did not report pre-existing cardiac disorders.

Reminder of advice to minimise risk

The risk of cardiac failure with carfilzomib is increased in elderly patients (those aged 75 years and older) and in Asian patients.

Although adequate hydration is required before starting treatment (see [Summary of Product Characteristics](#)), all patients should be monitored for evidence of volume overload, especially patients at risk of cardiac failure.

Patients with marked or severe cardiac failure (New York Heart Association [NYHA] Class III and IV), recent history of myocardial infarction (in the last 4 months), and patients with uncontrolled angina or arrhythmias should have a comprehensive medical assessment before starting treatment with carfilzomib. Particular attention should be given to the control of blood pressure and fluid management and patients should remain under close follow-up during treatment.

Stop carfilzomib if severe or life-threatening cardiac events occur. Restarting of treatment may be considered at a lower dose once the condition is controlled and the patient is functionally stable.

Pulmonary hypertension has also been reported in patients treated with carfilzomib and patients should be evaluated as appropriate.

Report adverse drug reactions on a Yellow Card

Carfilzomib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse drug reactions (ADRs) to drugs under additional monitoring 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 today via [iTunes Yellow Card](#) for iOS devices or via [PlayStore Yellow Card](#) for Android devices.

Article citation: Drug Safety Update volume 13, issue 1: August 2019: 3.

Letters and drug alerts sent to healthcare professionals in July 2019

Letters

The following letters were sent to healthcare professionals in July 2019:

- [Oncaspar ▼ \(pegaspargase\): Irish packs made available to UK market](#)
- [Ketalar \(ketamine\) injection: interim supply from Ireland to mitigate supply disruption](#)
- [Elmiron \(pentosan polysulfate sodium\): risk of pigmentary maculopathy](#)

Recall alerts for medicines taken out of the supply chain during distribution

Following the issue of [FMD Alert EL \(19\)A/15](#) on 27 June 2019, MHRA has become aware of further affected products that were imported into the UK from Italy and re-labelled in Kosei Pharma UK Ltd, MPT Pharma Ltd, Drugsrus Ltd / P.I.E. Pharma Ltd and Doncaster Pharmaceuticals Group Ltd livery.

A new recall alert was issued on 25 July 2019 – [FMD Alert: Class 2 \(EL \(19\)A/19\)](#).

Products being recalled at patient level are:

- Neupro 4mg/24hr patches
- Vimpat 100mg tablets

If patients have any of these affected products, they are advised to continue taking their medicines and contacting their prescriber to **arrange a new** prescription. Patients should return the affected batches to their pharmacist once they have a new prescription.

The products being recalled at pharmacy level are:

- Dovobet gel
- DuoResp Spiromax 160mcg / 4.5mcg inhaler
- Incruse Ellipta 55mcg Inhaler
- Seretide Evohaler 250mcg
- Spiriva 18mcg inhalation powder capsules

Patients with the products being recalled at pharmacy level should continue taking their medicines. They do not need to arrange a new prescription but are advised to speak to a healthcare professional if they have any questions.

Other alerts

[Class 2 Medicines Recall: Bisacodyl 5mg Gastro-Resistant tablets batch 25074A \(MDR 34-04/19\)](#). Issued 24 July 2019. The [listed batch](#) has been recalled because a small number of packs have been found to contain tablets which are stuck together, with mould observed on some tablets. It is unlikely that affected tablets will have got to patient level as the sticking is noticeable on opening the pack, nevertheless, batch 25074A should be quarantined and returned to the supplier.

[Class 2 Medicines Recall: Aripiprazole 1mg/ml oral solution \(EL \(19\)A/20\).](#)

Issued 30 July 2019. [Listed batches](#) have been recalled due to the potential for small particles of Aripiprazole active material to be present, which could affect the efficacy of the product. No relevant product complaints or adverse reaction reports have been received by the company from the UK market to date.

[Class 4 Medicines Defect Information: Phenobarbital Sodium 30mg/ml Injection \(MDR 48-02/19\).](#)

Issued 8 July 2019. The EAN bar code for the [listed batches](#) is incorrect, which increases the risk of medication error due to product mix-up when an automated inventory system is used to dispense the affected batch within the pharmacy or wholesale facility. The barcode should not be used for any dispensing activities for the listed batches.

Healthcare professionals are also reminded of the caution in use notice issued for [Emerade adrenaline autoinjectors](#). Prescribers and dispensers should inform patients of the very rare risk of the product failing to deliver a dose of adrenaline from the syringe due to blockage of the needle. Healthcare professionals should continue to reinforce that patients should always carry TWO in-date adrenaline auto-injectors with them. For more information, see [Drug Safety Update, July 2019](#).

Article citation: Drug Safety Update volume 13, issue 1: August 2019: 4.

Medical Devices Alerts issued in July 2019

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

[Automated external defibrillators: All Telefunken HR1 & FA1 – no valid CE certificate \(MDA/2019/027\).](#)

Issued 25 July 2019. Manufactured by Defiteq International BV or GGT Holding BV. The safety and performance of these devices cannot be verified, and their safe use can no longer be assured. It is recommended that organisations initiate a process to source an alternative defibrillator.

[Professional use capillary blood specimen collection: BD Microtainer tubes – risk of blood leakage and/or incorrect test results due to defective tubes.](#)

Issued 24 July 2019. Manufactured by Becton Dickinson (BD). Tubes may contain a hole or be damaged or deformed, potentially causing blood leakage and/or an inadequate blood-to-additive ratio, leading to incorrect test results. In these cases, re-sampling could lead to a delay in treatment. It is recommended to inspect inventory for the [devices listed in the notice](#) and return or destroy any device affected.

Article citation: Drug Safety Update volume 13, issue 1: August 2019: 5.
