

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

Volume 11 Issue 6 January 2018

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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.



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/

In our first article this month, we have important new advice about the multiple sclerosis medicine daclizumab (daclizumab beta; Zinbryta ▼) following a European review of the risk of severe liver injury (page 2). Note carefully and act on the new restricted indication, contraindications and warnings, and monitoring requirements. Review any patient receiving daclizumab to check that this treatment remains appropriate and ensure they understand the risks before continuing or initiating daclizumab.

In our second article, we advise you of a very rare risk of severe cutaneous adverse reactions associated with recombinant human erythropoietins (page 4). Discontinue erythropoietins permanently if a patient develops a severe cutaneous adverse reaction such as Stevens-Johnson syndrome or toxic epidermal necrolysis.

Next, we remind you to be vigilant for drug names that sound-like or look-like others in light of recent cases of medication error relating to drug-name confusion (page 6).

In our fourth article, note the prescribing and dispensing recommendations related to minimising risk of medication error and accidental overdose with co-dydramol following the launch of new products containing 20 mg and 30 mg of dihydrocodeine (page 7).

Finally, we continue our campaign to support reporting of suspected adverse drug reactions to the Yellow Card Scheme with a reminder to ask patients about any herbal medicines they are taking and to report any suspected side effects (page 8).

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Daclizumab (Zinbryta ▼) and risk of severe liver injury: new restrictions to use and strengthened liver monitoring

The use of daclizumab (daclizumab beta) is now restricted to adults with relapsing multiple sclerosis who have had an inadequate response to at least 2 other disease-modifying therapies (DMTs) and for whom other DMTs are contraindicated or unsuitable. Do not use daclizumab in patients with pre-existing hepatic disease or hepatic impairment. Discuss with patients the risk of hepatic injury and the liver monitoring requirements before starting or continuing daclizumab and ask them to sign an acknowledgement form to confirm they understand the information.

Advice for healthcare professionals:

Restricted indication

- daclizumab (daclizumab beta) should only be prescribed in adults with relapsing multiple sclerosis who have had an inadequate response to at least 2 other disease-modifying therapies (DMTs) and for whom other DMTs are contraindicated or unsuitable; do not use in patients with pre-existing hepatic disease or hepatic impairment
- review any patient currently receiving daclizumab to check that treatment remains appropriate

New precautions for use

- screen patients for hepatitis B and C viral infections before starting daclizumab and refer those with evidence of infection to a liver specialist for advice
- initiation is not recommended in patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels equal to or greater than 2-times the upper limit of normal or in those with autoimmune conditions other than multiple sclerosis
- exercise caution when prescribing daclizumab in patients receiving other medication that may be hepatotoxic, including over-the-counter products and herbal medicines

Revised liver monitoring requirements

- monitor ALT, AST, and bilirubin levels closely before each dose (or more frequently if clinically indicated); and continue monitoring for up to 6 months after the last dose (see monitoring requirements below)

Updated hepatic risk management programme

- discuss risk of hepatic injury and monitoring requirements with patients and ensure they read the patient card; both patient and physician should sign an acknowledgement form to confirm that the discussion has taken place and the patient understands the information that has been given to them
- advise patients to seek urgent medical attention if they develop any symptoms or signs of potential hepatic injury

[Daclizumab \(Zinbryta ▼\) and risk of severe liver injury: initiation in multiple sclerosis now restricted, promptly review patients already on treatment.](#)

Drug Safety Update, July 2017.

Restricted indication and new precautions for use

In July 2017, we highlighted [restrictions on the use of daclizumab \(Zinbryta ▼\)](#) for relapsing multiple sclerosis during an urgent EU review into the risk of severe liver injury. The review found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with daclizumab and for up to 6 months after discontinuation. Serious liver reactions, including autoimmune hepatitis, hepatitis, and jaundice, were observed in 1.7% of patients taking daclizumab in clinical trials.

[EMA concludes review of Zinbryta and confirms further restrictions to reduce risk of liver damage.](#)

Direct Healthcare Professional Communication. [Zinbryta▼ \(daclizumab\): restrictions of use due to the risk of fulminant liver failure.](#) 29 November 2017.

Following the review's [conclusions](#), daclizumab should only be started in adult patients with relapsing forms of multiple sclerosis who have had an inadequate response to at least 2 other disease-modifying therapies (DMTs) and for whom treatment with any other DMT is contraindicated or unsuitable.

Review any patient receiving daclizumab and stop treatment if they are not within this revised indication or if treatment is contraindicated. Also, consider stopping treatment if an adequate response has not been achieved or if the patient does not comply with the necessary liver monitoring (below).

Revised liver monitoring requirements

Check liver function tests (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin levels) at least monthly as close as possible before each dose, or as often as clinically indicated during treatment, and for up to 6 months after the last dose of daclizumab. Treatment discontinuation is recommended if ALT or AST levels exceed 3 times the upper limit of normal; refer the patient to a liver specialist for advice promptly.

Monitor patients closely for signs and symptoms of hepatic injury. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction, promptly measure serum transaminases, discontinue treatment with Zinbryta, as appropriate, and refer patients urgently to a liver specialist.

Updated hepatic risk management programme

The hepatic risk management guide for physicians and patient card will be updated with detailed information on the risk of severe liver injury and the revised monitoring requirements. Provide patients with the patient card and discuss with them the risk of hepatic injury and necessary monitoring requirements before prescribing daclizumab. Both the patient and physician should sign the acknowledgement form to confirm that the discussion has taken place and that the patient understands the information that has been given to them.

Advise patients to seek medical attention immediately if they develop any signs and symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, tiredness, loss of appetite, yellowing of the skin and eyes, or dark urine.

Background

[Daclizumab \(Zinbryta▼\) 150 mg solution for injection](#) was authorised in the EU in July 2016 for the treatment of adults with relapsing forms of multiple sclerosis. Daclizumab has mainly been used in clinical trials in the UK and use outside trials has been small to date.

Call for reporting

Daclizumab (Zinbryta▼) is subject to additional monitoring to allow quick identification of new safety information. Report any suspected adverse reactions (ADRs) promptly to the [Yellow Card Scheme](#).

Article citation: Drug Safety Update volume 11 issue 6; January 2018: 1.

[Summary of Product Characteristics. Zinbryta▼.](#)

Recombinant human erythropoietins: very rare risk of severe cutaneous adverse reactions (SCARs)

Recombinant human erythropoietin (r-HuEPO) treatment has been associated with very rare cases of life-threatening severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Withdraw r-HuEPOs permanently in patients who develop severe skin reactions such as SJS or TEN.

Advice for healthcare professionals:

- we are aware of very rare cases of severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients receiving recombinant human erythropoietins (r-HuEPOs); some cases were fatal
- more severe cases were recorded with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta)
- advise patients of the signs and symptoms of severe skin reactions at initiation and instruct them to stop treatment and seek immediate medical attention if they develop widespread rash and blistering; these rashes often occur following fever or flu-like symptoms
- discontinue all r-HuEPOs permanently in patients who develop severe cutaneous adverse reactions such as SJS or TEN
- report all suspected adverse reactions to HuEPOs on a [Yellow Card](#)

Background

Recombinant human erythropoietins (r-HuEPOs) stimulate erythropoiesis and are indicated for the treatment of anaemia in patients with chronic kidney disease. Some r-HuEPOs are also authorised for the treatment of anaemia after chemotherapy for non-myeloid cancer; in premature babies; and in adults needing autologous blood transfusion during surgery.

The following 5 r-HuEPOs (with brand leaders) are authorised in the UK:

- epoetin alfa (Eprex)
- darbepoetin alfa (Aranesp, a hyperglycosylated epoetin derivative)
- epoetin beta (NeoRecormon)
- epoetin zeta (Retacrit)
- methoxy polyethylene glycol-epoetin beta (Mircera)

Very rare risk of severe cutaneous adverse reactions

The long-acting r-HuEPO methoxy polyethylene glycol-epoetin beta (Mircera) has been associated with a risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) following a case report in 2014 about a patient with anaemia in chronic renal failure who experienced severe mucosal eruptions 5 days after the first dose of Mircera.¹ The patient improved with corrective treatment but symptoms re-occurred following a second dose. Warnings for severe cutaneous adverse reactions (SCARs) have been present in the product information for Mircera since 2015.

1. Mesonjesi E, et al. [Stevens-Johnson syndrome or toxic epidermal necrolysis induced by erythropoietin](#). *Allergy* 2014; **69** (suppl): abstract 1594.

A 2017 European review triggered by post-marketing reports of severe cutaneous reactions (see below) concluded that the class of r-HuEPOs is associated with a risk of SCARs, including SJS and TEN. The exact frequency of these reactions could not be calculated but they are understood to occur very rarely.

The product information of all r-HuEPOs is being updated to reflect the risk of SCARs and to advise healthcare professionals and patients to permanently discontinue r-HuEPOs should these reactions occur.

Data summary

The review assessed all cases worldwide received up to February 2017, and identified a total of 23 reports of SJS and 14 reports of TEN with r-HuEPOs. At least 1 case of SJS and TEN was reported with each of the following erythropoietins: darbepoetin alfa, epoetin alfa, epoetin beta, and methoxy polyethylene glycol-epoetin beta. The review concluded that 8 reports of SJS and 1 case of TEN were causally associated with r-HuEPOs. More severe cases were observed with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta). No cases were identified with epoetin zeta; however, the review concluded that the risk of severe cutaneous adverse reactions was a class effect with all r-HuEPOs.

Signs and symptoms of SJS and TEN

1. Flu-like symptoms including fever, tiredness, muscle, and joint pain
2. Widespread rash with reddening and blistering of the skin and oral mucosa, eyes, nose, throat, or genital area
3. Peeling and shedding of the affected skin, which looks like a severe burn

Call for reporting

Please continue to report suspected adverse reactions to r-HuEPOs on a [Yellow Card](#).

Further information

Direct Healthcare Professional Communication. [Recombinant human erythropoietins: Risk of severe cutaneous adverse reactions](#). 30 September 2017.

NHS Choices. [Stevens-Johnson syndrome](#).

Article citation: Drug Safety Update volume 11, issue 6; January 2018: 2.

Drug-name confusion: reminder to be vigilant for potential errors

Take particular care when prescribing or dispensing medicines that could be confused with others (ie, they sound-alike or look-alike).

Advice for healthcare professionals:

- be extra vigilant when prescribing and dispensing medicines with commonly confused drug names to ensure that the intended medicine is supplied
- if pharmacists have any doubt about which medicine is intended, contact the prescriber before dispensing the drug
- follow local and professional guidance in relation to checking the right medicine has been dispensed to a patient
- report suspected adverse drug reactions where harm has occurred as a result of a medication error on a [Yellow Card](#) or via local risk management systems that feed into the [National Reporting and Learning System](#)

We are aware of recent cases, including cases with fatal outcomes, in which patients have received the wrong medicine due to confusion between similarly named or sounding brand or generic names. Since our last Drug Safety Update on [drug-name confusion](#) in 2013, we have received Yellow Card reports of harm following confusion between the drugs listed in the table below. See the [Drug Safety Update in April 2013](#) for more examples.

[Recent drug-name confusion. Drug Safety Update, April 2013.](#)

Clobazam (benzodiazepine)	Clonazepam (antiepileptic drug)
Atenolol (beta blocker)	Amlodipine (calcium channel blocker)
Propranolol (beta blocker)	Prednisolone (corticosteroid)
Risperidone (antipsychotic)	Ropinirole (dopamine agonist)
Sulfadiazine (antibiotic)	Sulfasalazine (disease-modifying anti-rheumatic drug)
Amlodipine (indicated for hypertension and angina)	Nimodipine (indicated for the prevention of ischaemic neurological deficits following aneurysmal subarachnoid haemorrhage)

Double checking when prescribing or administering any medicines is important to avoid any medication errors. You can double check it is the:

- right medicine
- right patient
- right dose
- right route
- right time

Suspected adverse drug reactions, including those arising from medication errors, should be reported on a [Yellow Card](#) or via local risk management systems that feed into the [National Reporting and Learning System](#) (NRLS). If reported to the NRLS, reports will be shared with the MHRA. In the absence of harm, errors should be reported through local reporting systems. Report any look-alike, sound-alike errors to MHRA via patient.information@mhra.gov.uk.

Article citation: Drug Safety Update volume 11 issue 6; January 2018: 3.

Co-dydramol: prescribe and dispense by strength to minimise risk of medication error

Previously co-dydramol (dihydrocodeine/paracetamol) was available only in the ratio 1:50 (co-dydramol 10/500 mg). Two products are now available with a higher strength of dihydrocodeine (co-dydramol 20/500 mg and 30/500 mg tablets). It is therefore important that co-dydramol products are prescribed and dispensed by strength to minimise dispensing errors and the risk of accidental opioid overdose.

Advice for healthcare professionals:

- new co-dydramol products are available with a higher dose of dihydrocodeine (co-dydramol 20/500 mg and co-dydramol 30/500 mg tablets)
- when prescribing co-dydramol, clearly indicate tablet strength and dose
- when dispensing co-dydramol, ensure patients receive the prescribed strength of co-dydramol, and, if in doubt, contact the prescriber
- report suspected adverse drug reactions with opioids, including any harm from medication error, via the [Yellow Card Scheme](#)

The ratio of dihydrocodeine to paracetamol in co-dydramol was previously fixed at 1:50 (ie, 10 mg/500 mg). Marketing authorisations have recently been approved for co-dydramol 20 mg/500 mg tablets and co-dydramol 30 mg/500 mg tablets.

The packaging for different co-dydramol products has been designed to clearly differentiate between the strengths. However, you should be vigilant when prescribing and dispensing to ensure patients receive the correct dose of dihydrocodeine.

New products are only just becoming available and we have not received any Yellow Card reports of dosing error with new formulations of co-dydramol. If a dosing error occurs and a patient has signs of opioid toxicity, consult the Summary of Product Characteristics and follow local care guidance for opioid overdose. Instruct patients to always read the leaflet that accompanies their medicine and to never exceed the recommended dose.

Article citation: Drug Safety Update volume 11 issue 6; January 2018: 4.

Herbal medicines: report suspected adverse reactions to the Yellow Card Scheme

If an adverse reaction is suspected, ask patients whether they are taking any herbal medicines and discuss with them the importance of reporting this via the Yellow Card Scheme.

Advice for healthcare professionals:

- remember, if an adverse reaction is suspected [it is important to ask patients if they are taking any herbal medicines](#)
- report suspected adverse reactions to herbal medicines, including traditional Chinese medicines, via the [Yellow Card Scheme](#)
- when submitting a Yellow Card for herbal medicines, it is important that you provide some extra details to help us to identify the particular product (see details below)
- advise patients to check for the Traditional Herbal Registration Certification Mark

Report suspected adverse reactions to the Yellow Card Scheme

The [Yellow Card Scheme](#) is vital in helping the MHRA monitor the safety of all healthcare products in the UK. Over the next year, we will be publishing regular short articles to highlight how you can support the safety of medicines in the UK by reporting suspected adverse drug reactions to the Yellow Card Scheme. This article focuses on herbal medicines, including traditional Chinese medicines.

[Research commissioned by MHRA in 2008](#) indicated that approximately a third of UK adults had used herbal medicines. These products have the potential to cause adverse reactions as well as interact with conventional medicines.

Reporting of Yellow Cards has led to important warnings about herbal medicines, for example the following Drug Safety Updates:

- [St John's wort interaction with the efficacy of hormonal contraceptives, including implants](#)
- [Traditional Chinese medicines containing lei gong teng \(tripterygium wilfordii\): risk of serious side effects, including impaired fertility](#)

Healthcare professionals and patients can report any suspected side effects or adverse reactions to herbal medicines using the [Yellow Card Scheme](#). When submitting a Yellow Card for herbal medicines, it is important that you provide some extra details to help us to identify the particular product, such as:

- the brand name (if it has one)
- the list of ingredients
- ideally, a copy of package labelling (emailed to yellowcard@mhra.gov.uk)
- details of the manufacturer

Look out for the Traditional Herbal Registration certification mark

More and more products are being registered under the [Traditional Herbal Registration \(THR\) Scheme](#).

Tell patients to always look out for the THR logo on the label and discuss with them that this means the herbal medicine has been registered with the MHRA and was found to meet standards of quality, safety, and patient information. A list of registered herbal medicines can be found [online](#).



Further information

NHS Choices. [Herbal medicines](#).

Article citation: Drug Safety Update volume 11 issue 6; January 2018: 5.

Letters sent to healthcare professionals in December 2017

In December 2017, the following letters were sent to relevant healthcare professionals:

- Cladribine (Litak and Leustat): [risk of progressive multifocal leukoencephalopathy \(PML\)](#)
- Radium-223-dichloride (Xofigo ▼): [increased risk of death and fractures in a randomised clinical trial with Xofigo used in combination with abiraterone acetate and prednisolone/prednisone](#)
- Vials of ERWINASE from batch 183a, 184a and 185a* [should be used with a 5-micron filter needle](#)

Article citation: Drug Safety Update volume 11 issue 6; January 2018: 6.

Medical Device Alerts issued in December 2017

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](#).

Alert were recently issued by MHRA about:

- Syringe pumps – [required user actions in the event of PL3 alarm to prevent risk of interrupted infusion](#)
- Nasogastric (NG) feeding tubes – [recall due to risk of neonatal or paediatric patient choking on ENFIT connector cap](#)

Article citation: Drug Safety Update volume 11 issue 6; January 2018: 7.
