

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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This month we inform you of important new information regarding the risk of serious liver injury with daclizumab (Zinbryta ▼), licensed for relapsing multiple sclerosis (page 2). While an urgent EU-wide review of liver safety is ongoing, review promptly any patients who are currently taking daclizumab to assess whether this medicine continues to be appropriate for them. Note that initiation of new patients is now restricted to two particular multiple sclerosis patient groups with limited treatment options and all patients should have close liver function monitoring.

We have an article on reports of increased mortality with bendamustine (Levact) when used in combination treatments outside the approved indications (page 4). Post-marketing data suggest that the risk of opportunistic infections associated with bendamustine may be greater than previously recognised. Monitor patients for signs and symptoms of infections throughout treatment, including hepatitis B reactivation. Also, you should be clear on your responsibilities when prescribing off-label or unlicensed medicines.

Additionally, we feature reports of possible organ transplant rejection with nivolumab (Opdivo ▼) or pembrolizumab (Keytruda ▼), which are used to treat various types of cancer, when used in transplanted patients (page 7). The benefit of treatment with nivolumab or pembrolizumab versus the risk of possible organ rejection should be considered in these patients.

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

While an urgent EU-wide review of new information on liver safety is under way, promptly review patients on treatment. Only initiate daclizumab in restricted groups of patients with limited treatment options and keep all patients under close liver function monitoring.

Review of patients

Healthcare professionals should review promptly any patients who are currently taking daclizumab to assess whether this medicine continues to be appropriate for them. This should include a discussion with the patient of the risks.

Consider discontinuing therapy if the patient is not within the restricted indication (see below) or if an adequate response has not been achieved.

Doctors should monitor liver function (serum transaminase levels and bilirubin levels) as often as clinically indicated, at least monthly, both during treatment and for up to 4 months after the last dose of patients receiving daclizumab.

Closely watch patients for signs and symptoms of hepatic injury.

If there is evidence of hepatic injury (either clinically or laboratory), treatment should be stopped and the patient should be promptly referred to a hepatologist.

Restrictions on use

Treatment with daclizumab (Zinbryta ▼) should now only be initiated in patients in the following restricted groups:

- highly active relapsing multiple sclerosis that has failed to respond to at least one disease-modifying therapy
- severe relapsing multiple sclerosis unsuitable for treatment with other disease-modifying therapies

Treatment with daclizumab is now contraindicated in patients with pre-existing hepatic disease or hepatic impairment. Treatment initiation is not recommended in patients with alanine transaminase or aspartate aminotransferase 2 or more times the upper limit of normal.

Treatment initiation is not recommended in patients with a history of concurrent autoimmune conditions (except for multiple sclerosis). Caution should be used when concomitantly administering medicinal products of known hepatotoxic potential, including non-prescription products and herbal supplements.

Background

Daclizumab (Zinbryta ▼) 150 mg solution for injection was authorised in the EU in July 2016 for adults with relapsing forms of multiple sclerosis. In the UK to date, daclizumab use has been mainly in clinical trials.

[The National Institute for Health and Care Excellence \(NICE\)](#) and [The Scottish Medical Consortium](#) issued treatment recommendations for daclizumab in April 2017.

Urgent Europe-wide review of new information on risk of liver injury with daclizumab

An urgent EU-wide review of daclizumab started after the death from liver injury (fulminant liver failure) of a patient involved in an ongoing observational study, as well as 4 cases of serious liver injury.

The risk of liver damage with daclizumab was already known at time of its approval in the EU. Several measures are already in place to manage this risk, including the requirement to monitor liver function regularly, and educational materials for healthcare professionals and patients on the risk of liver damage. However, the fatal case occurred despite compliance with the recommended liver monitoring and with test results that were within the normal range prior to and during treatment.

Reminder of existing advice about risk of liver injury

Discuss the risk of hepatic injury with patients and provide them with a Patient Card.

Advise patients to contact their doctor immediately if they develop any symptoms of liver problems, such as unexplained nausea (feeling sick), vomiting, abdominal pain, tiredness, loss of appetite, yellowing of the skin and eyes, and dark urine.

In case of elevations of transaminases or total bilirubin, treatment interruption or discontinuation may be required; see table below from the summary of product characteristics for Zinbryta (daclizumab).

Test result	Summary of action required
Confirmed ALT or AST >5 x ULN <i>or</i> Confirmed ALT or AST >3 x ULN and bilirubin >2 x ULN	Treatment discontinuation*
ALT or AST >3 x ULN	Treatment interruption and close monitoring Resume when ALT or AST have reached <2 x ULN

Table: Summary of action required as a result of liver function test results¹

1. [Zinbryta](#), summary of product characteristics

*Re-initiation of therapy may be considered if other aetiologies are found, values have returned to normal, and benefits to the patient of resuming therapy outweigh the risks.

ALT: alanine aminotransferase. AST: aspartate aminotransferase. ULN: upper limit of normal.

Next steps

Relevant healthcare professionals are being informed by letter about the need to promptly review patients currently on treatment, and to initiate daclizumab only in a restricted group of multiple sclerosis patients with limited treatment options who should be kept under close liver function monitoring.

We will provide further information as soon as this review is completed. For more about the review timetable see the [European Medicines Agency](#) website.

Further information

[Letter to The Association of British Neurologists](#)

[EMA restricts use of multiple sclerosis medicine Zinbryta](#)

Article citation: Drug Safety Update volume 10 issue 12, July 2017: 1.

Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatitis B reactivation

Recent clinical trials have shown increased mortality when bendamustine (Levact) was used in combination treatments outside its approved indications. Be aware that the risk of opportunistic infections for all patients receiving bendamustine including those receiving off-label treatment may be greater than previously recognised. Be aware of your responsibilities if prescribing bendamustine outside the licensed indications.

Advice for healthcare professionals:

- advise patients to report promptly new signs of infection, including fever or respiratory symptoms, and consider discontinuing bendamustine if there are signs of opportunistic infections
- monitor patients for opportunistic infections as well as cardiac, neurological, and respiratory adverse events
- hepatitis B virus (HBV) reactivation has also been reported; monitor known carriers of HBV for signs and symptoms of active HBV infection.
- increased mortality (mainly due to opportunistic infections) was observed in recent clinical studies when bendamustine was used in combination treatment outside the approved indications
- report suspected adverse reactions associated with bendamustine to us on a [Yellow Card](#)

Background

Bendamustine is indicated for:

- first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate
- indolent non-Hodgkin's lymphomas as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab-containing regimen
- front-line treatment of multiple myeloma (Durie-Salmon stage II with progression or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at the time of diagnosis limiting the use of thalidomide or bortezomib-containing treatment

Recent clinical trial findings

1. Flinn IW, et al. [Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study](#). *Blood* 2014; 123: 2944–52.
2. Sehn LH, et al. [Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma \(GADOLIN\): a randomised, controlled, open-label, multicentre, phase 3 trial](#). *Lancet Oncol* 2016; 17: 1081–93.

In clinical trials^{1,2} of non-approved combination therapies, bendamustine was associated with increased mortality and an unfavourable safety profile when used in combination with rituximab or obinutuzumab.

Deaths were mainly due to infections including bacterial (sepsis, pneumonia) and opportunistic infections such as *Pneumocystis jirovecii* pneumonia, varicella zoster virus, and cytomegalovirus infection. Some fatal cardiac, neurological, and respiratory toxicities were also reported.

Post-marketing data

Opportunistic infections

A recent European review of post-marketing data has suggested that the risk of opportunistic infections with bendamustine treatment may be greater than previously recognised.

Consult the revised [summary for product characteristics](#) and be aware of updated warnings regarding infections.

Infections include bacterial (sepsis, pneumonia) and opportunistic infections such as *Pneumocystis jirovecii* pneumonia, varicella zoster virus, and cytomegalovirus infection.

Both the frequency and outcome of infections seem to be highly variable and dependent on the clinical setting. High frequencies of opportunistic infections may be linked to lymphocytopenia and low CD4-positive T-cell counts. Lymphocytopenia (<600 cells per μL) and low CD4-positive T-cell counts (<200 cells per μL) lasting at least 7–9 months after treatment with bendamustine has been reported in a significant portion of patients. Lymphocytopenia and CD4-positive T-cell depletion are thought to be more pronounced when bendamustine is combined with rituximab.

You should:

- monitor patients for respiratory signs and symptoms throughout treatment
- advise patients to report new signs of infection, including fever or respiratory symptoms promptly
- consider discontinuing bendamustine if there are signs of opportunistic infections

Hepatitis B virus reactivation

Reactivation of hepatitis B virus in chronic carriers of the virus has been reported after bendamustine. Some cases resulted in acute hepatic failure or a fatal outcome. Closely monitor carriers of hepatitis B virus for signs and symptoms of active infection.

Prescribing off-label or unlicensed medicines

Refer to [prescribers' responsibilities for off-label or unlicensed use of medicines](#).

Reporting of suspected adverse reactions

Suspected adverse reactions should be reported to us on a [Yellow Card](#) including those associated with use outside the licence.

Further information

[Letter sent to healthcare professionals](#)

[Levact](#) (bendamustine) summary of product characteristics

Article citation: Drug Safety Update volume 10 issue 11, July 2017: 2.

Nivolumab (Opdivo ▼), pembrolizumab (Keytruda ▼): reports of organ transplant rejection

There have been reports of rejection of solid organ transplants in patients treated with nivolumab or pembrolizumab. Ipilimumab (Yervoy ▼) may also interfere with immunosuppressive therapy, increasing the risk of graft rejection.

Advice for healthcare professionals:

- rejection of solid organ transplants, including renal and corneal grafts, has been reported in the post-marketing setting in patients treated with programmed death receptor 1 (PD-1) inhibitors
- consider the benefit of treatment with nivolumab or pembrolizumab versus the risk of possible organ transplant rejection for each patient
- some cases of rejection occurred in association with ipilimumab, which carries a warning that it may interfere with immunosuppressive therapy, resulting in an increased risk of graft rejection

Background

Nivolumab (Opdivo ▼) and pembrolizumab (Keytruda ▼) are immune checkpoint inhibitors that specifically block the activity of a protein called programmed death receptor 1 (PD-1).

These drugs are indicated for the treatment of various cancer types, including malignant melanoma, non-small-cell lung cancer, and relapsed or refractory classical Hodgkin's lymphoma. For more information on the authorised indications, see the summaries of product characteristics for [nivolumab](#) and [pembrolizumab](#).

Data summary

A European review of worldwide data concluded that nivolumab and pembrolizumab may increase the risk of rejection in organ transplant recipients.

The review assessed all cases received up to November 2016 and identified 9 patients who had transplant rejection after receiving nivolumab and pembrolizumab.

Of the 5 patients receiving nivolumab, 3 had kidney transplant rejection, 1 had corneal transplant rejection, and 1 had skin graft rejection.

Four patients receiving pembrolizumab had kidney transplant rejection; 2 patients were diagnosed after biopsy.

Ipilimumab

[Ipilimumab](#) (Yervoy ▼), another immune checkpoint inhibitor, specifically blocks the activity of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and is indicated for malignant melanoma.

In 2 of the 9 reports of rejection, patients started treatment with ipilimumab before receiving nivolumab or pembrolizumab. Ipilimumab is known to increase the risk of graft rejection.

Call for reporting

Please continue to report any suspected adverse reactions to nivolumab, pembrolizumab, and ipilimumab on a [Yellow Card](#).

Article citation: Drug Safety Update volume 10 issue 12, July 2017: 3.

Letters sent to healthcare professionals in June 2017

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

- Arsenic Trioxide (Trisenox) 1 mg/mL concentrate for solution for infusion: [importation and over-labelling of United States \(US\) Trisenox stock as Teva UK interim supply](#)
- Upravi ▼ (selexipag): [concomitant use with strong CYP2C8 inhibitors \(eg, gemfibrozil\) now contraindicated](#)
- Cinryze ▼ (C1 esterase inhibitor [human]): recommendations to prescribers in view of a [potential supply shortage](#)
- DepoCyte (cytarabine): [follow-up on EU supply issue](#)
- Clexane (enoxaparin sodium): [updates to strength expression, dose regimens in DVT/PE, use in patients with severe renal impairment](#)

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Medical Device Alerts issued in June 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](#).

Medical Device Alerts were recently issued by MHRA about:

- Unomedical high concentration oxygen masks (specific lots): [risk of hypoxia as the tubing can disconnect from the oxygen mask](#)
- All metal-on-metal (MoM) hip replacements: [updated advice for follow-up of patients](#)
- BVM (Bag-Valve-Mask) manual resuscitation systems, manufactured by Intersurgical: [risk of delay to emergency treatment](#)

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