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HPRA DRUG SAFETY NEWSLETTER

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In this Edition

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

An urgent EU-wide review of daclizumab was commenced 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. While this safety review is ongoing, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has restricted the initiation of daclizumab (Zinbryta) and recommends that all currently treated patients are promptly reviewed. Whilst the review is ongoing daclizumab should only be initiated in restricted groups of patients with limited treatment options and all patients should be kept under close monitoring.

Background to the Review and Provisional Measures to Protect Patient Health

Daclizumab is an immunomodulatory interleukin inhibitor which was authorised centrally in the EU in July 2016 for the treatment of relapsing forms of multiple sclerosis (RMS) in adult patients. In Ireland, the use to date has been primarily in the context of clinical trials, and national post marketing experience is limited. The risk of liver damage with daclizumab was known at the 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 the provision of educational materials for healthcare professionals and patients on the risk of liver damage and how to prevent or reduce liver injury. 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. This is in the context of other reports of serious hepatic injury in clinical trials and post marketing, including a fatal case of autoimmune hepatitis during the trials. The PRAC has accordingly recommended provisional measures for daclizumab, to protect patient health, whilst the more comprehensive review of the benefits and hepatic risks is ongoing.

A Direct Healthcare Professional Communication (DHPC) was issued by the marketing authorisation holder (MAH) (following approval by the HPRA) in July 2017 to inform relevant healthcare professionals of the provisional measures. Following the completion of the ongoing review, the HPRA, in conjunction with our European counterparts, will communicate further and provide updated guidance for patients and healthcare professionals.

In the meantime, the following restrictions on use and monitoring requirements apply:

Restrictions on use

Treatment with daclizumab (Zinbryta) should now only be initiated in adult patients with relapsing forms of Multiple Sclerosis (RMS) in the following restricted groups:

- highly active relapsing multiple sclerosis that has failed to respond to at least one disease-modifying therapy
- rapidly evolving 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.

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Review of patients

Promptly review 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 above) 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 monitor patients for signs and symptoms of hepatic injury. If there is evidence of hepatic injury (either clinical or laboratory), treatment should be stopped and the patient should be promptly referred to a hepatologist.

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.

Key Message

While an urgent EU review of new information on liver safety is ongoing, promptly review patients on treatment.

Only initiate daclizumab in restricted groups of patients with limited treatment options.

Keep all patients under close liver function monitoring (serum transaminase and bilirubin levels) and advise your patient what to look out for.

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

Further details on daclizuma (Zinbryta) are available at www.ema.europa.eu/ema/

Gabapentin – respiratory depression without concomitant opioid use

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently concluded a review of respiratory depression associated with gabapentin use without concomitant opioid therapy.

Gabapentin-containing medicinal products are licensed in Ireland under various brand names for the treatment of specific forms of epilepsy and also for the treatment of peripheral neuropathic pain. The risk of central nervous system (CNS) depression such as somnolence, sedation and respiratory depression in association with concomitant use of gabapentin and opioids is already known and is detailed in the summary of product characteristics (SmPC) for gabapentin-containing medicinal products, where the potential for CNS depression, including respiratory depression, in patients who use gabapentin and morphine concomitantly as a result of increases in gabapentin concentrations is outlined. This warning in the SmPC includes a recommendation to reduce the dose of either opioids or gabapentin appropriately. However, having considered the available evidence including several cases where opioid use was not a factor in the occurrence of respiratory depression, the PRAC considered that gabapentin has also been associated with severe respiratory depression without concomitant opioid use and that the product information should be updated accordingly to reflect this risk and to advise healthcare professionals and patients/care-givers.

Patients with the following risk factors may be at higher risk of experiencing respiratory depression with gabapentin (without concomitant opioid use):

- Concomitant use with CNS depressants (other than opioids);
- Compromised respiratory function;
- Respiratory or neurological disease;
- Renal impairment;
- Elderly.

Advice to Healthcare Professionals

- Gabapentin without concomitant opioid use has been associated rarely with severe respiratory depression.
- Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing severe respiratory depression.
- Dose adjustments might be necessary in these higher risk patients.

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Key Message

Gabapentin has been associated with severe respiratory depression independent of concomitant opioid use. Dose adjustments may be necessary in higher risk patients.

Gabapentin-containing medicinal products include Gabin, Neurontin and Neurostil. Further details are available on www.hpra.ie

Amoxicillin; co-amoxiclav – very rare reports of DRESS (drug reaction with eosinophilia and systemic symptoms)

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed a signal of drug reaction with eosinophilia and systemic symptoms (DRESS) in association with amoxicillin and co-amoxiclav. It is already known that serious and occasionally fatal hypersensitivity reactions (including anaphylactoid reactions) have been reported in patients on penicillin therapy. Having considered the available evidence in EudraVigilance and in the literature, the PRAC considered that the product information for amoxicillin and co-amoxiclav containing medicinal products should be updated to extend warnings about the very rare occurrence of severe cutaneous adverse reactions (SCARs) with amoxicillin to include reference to DRESS (drug reaction with eosinophilia and systemic symptoms).

Advice to Healthcare Professionals

- Amoxicillin has been very rarely associated with severe cutaneous adverse reactions including DRESS (drug reaction with eosinophilia and systemic symptoms).
- Symptoms of DRESS include flu-like symptoms with a rash, fever, lymhadenopathy, and abnormal haematological findings (including eosinophilia and abnormal liver function tests).

Key Message

Amoxicillin has been associated with very rare reports of drug reaction with eosinophilia and systemic symptoms (DRESS).

Amoxicillin and co-amoxiclav containing medicinal products include Amoclav, Amoxil, Augmentin, Augmentin Duo, Clavamel Forte, Geramox, Germentin, Oramox, and Pinamox. Further details are available on www.hpra.ie.

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Imbruvica (ibrutinib)	Risk of hepatitis B reactivation: Hepatitis B virus status to be established before initiating treatment with Imbruvica
Injectable methylprednisolone products containing lactose	New contraindication for injectable methylprednisolone products containing lactose in patients allergic to cow's milk proteins treated for allergic conditions

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

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