

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 (Zinbryta) 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 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 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 should now only be initiated in adult patients with relapsing forms of multiple sclerosis 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 levels 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.

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 daclizumab (Zinbryta) are available at www.ema.europa.eu/ema/

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