29th November 2017

Zinbryta▼ (daclizumab): restrictions of use due to the risk of fulminant liver failure

Dear Healthcare Professional,

Biogen in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- Daclizumab treatment can cause unpredictable and potentially fatal immune-mediated liver injury.
- Daclizumab should only be used for the treatment of relapsing forms of multiple sclerosis (RMS) in adult patients who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with any other DMT is contraindicated or otherwise unsuitable.
- Patient serum transaminase and bilirubin levels should be monitored as close as possible before each administration during treatment and for up to 6 months after the last dose of daclizumab.
- Discontinuation is recommended in patients whose ALT or AST levels are >3 times the upper limit of normal (ULN) regardless of bilirubin levels.
- Patients should be informed about the risk of hepatic injury and the need for periodic monitoring. They should be warned about signs or symptoms suggestive of hepatic dysfunction before treatment is started.
- An acknowledgement form should be presented to all patients, including patients currently taking this medicine.

Background on the safety concern

Several cases of serious liver injury including cases of immune-mediated hepatitis and fulminant liver injury have been reported, despite compliance with the recommended risk minimisation measures, including monthly liver function monitoring. Serious reactions, including autoimmune hepatitis, hepatitis and jaundice, have been observed in 1.7% of patients in clinical trials.

The EMA review concluded that treatment with daclizumab is associated with an immune-mediated risk of unpredictable and potentially fatal liver injury. This risk can occur through treatment and up to 6 months after the last dose of daclizumab.

Physicians should promptly reconsider whether daclizumab continues to be an appropriate treatment for their patients currently taking this medicine. Treatment discontinuation should be considered for patients not responding to treatment or failing to follow the requirement for the monthly or more frequent liver test monitoring. In addition, prior to treatment initiation with daclizumab, patients should be screened for Hepatitis B and C. Patients who tested positive are recommended to be referred to a physician with expertise in the treatment of these conditions.

The Summary of Product Characteristics (SmPC) of daclizumab was updated in July 2017 to reflect provisional precautionary measures. Following the conclusion of the safety review by EMA, which

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further characterised the risk of hepatic injury, the SmPC is being updated to restrict the indication. Additional safety information about serious hepatic injury will be also included. The following previously issued guidance is unchanged:

- Daclizumab is contraindicated in all patients with pre-existing hepatic disease or hepatic impairment.
- Treatment initiation is not recommended in patients with concurrent autoimmune conditions and caution should be used when co-administering daclizumab with other hepatotoxic medicinal products, including non-prescription products and herbal supplements.
- Patients should be advised to look out for signs and symptoms of hepatic injury. In case of signs or symptoms suggestive of such injury, the patient should be promptly referred to a hepatologist.
- Treatment initiation is not recommended in patients with ALT or AST ≥ 2 times the ULN prior to treatment.

Educational materials will be updated with the present recommendations. In addition, it is essential that the patients are fully informed of the risks before making the decision to initiate treatment with daclizumab. For that reason, an acknowledgment form, aimed at ensuring patients have been adequately informed of the risks and provided the patient card by their treating physician, will be introduced.

Call for reporting

Zinbryta▼ (daclizumab) is subject to additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions (ADRs) to the Yellow Card Scheme.

It is easiest and quickest to report ADRs online via the Yellow Cards website - https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line:

  0800-731-6789 or
- by downloading and printing a form from the yellow card website (see link above)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Company contact point

Further information can be requested from Biogen by telephone (0800 008 7401), fax [+44 (0) 1628 501 010] or email (MedInfoUKI@biogen.com).

Annexes

Contact point details for further information are given in the product information of the medicinal product (SmPC and PIL) at http://www.ema.europa.eu/ema/.

Yours faithfully

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