



17th July 2017

Zinbryta▼ (daclizumab): restrictions of use in view of fatal fulminant liver failure

Dear Healthcare Professional,

Biogen in agreement with European Medicines Agency (EMA), and the Medicines and Healthcare products Regulatory Agency (MHRA), would like to inform you of interim recommendations for Zinbryta▼ (daclizumab) while a European review of the risk of liver injury is carried out.

Summary

Interim recommendations:

- Zinbryta (daclizumab) should only be used for the treatment of relapsing forms of multiple sclerosis (RMS) in adult patients:
 - with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT), or
 - with rapidly evolving severe relapsing multiple sclerosis who are unsuitable for treatment with other DMTs
- Daclizumab is now contraindicated in patients with pre-existing hepatic disease or hepatic impairment
- You should promptly reconsider whether daclizumab continues to be an appropriate treatment for any of your patients currently taking this medicine.
- 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.
- Patient serum transaminase levels and bilirubin levels should be monitored as often as clinically indicated (at least monthly) both during treatment and for up to 4 months after the last dose of daclizumab.
- Monitor all patients for signs and symptoms of hepatic injury and advise your patient what to look out for. In case of signs or symptoms suggestive of such injury, the patient should be promptly referred to a hepatologist.
- Consider discontinuing therapy if an adequate therapeutic response has not been achieved.

Background on the safety concern

These recommendations are interim measures issued while the EMA is reviewing the medicine Zinbryta (daclizumab), which is indicated for the treatment of relapsing forms of multiple sclerosis (RMS) in adult patients. The review was initiated following a fatal case of fulminant liver failure in a patient treated with Zinbryta in an ongoing observational study. This case occurred despite compliance with the recommended risk minimisation measures, including liver function monitoring. In addition, further cases of serious liver injury have been reported.



The risk of liver injury with daclizumab was already known at time of its approval in the European Union in July 2016, and several measures have been taken to manage this risk, including the provision of educational materials for healthcare professionals and patients on how to prevent or reduce liver injury.

Further details about the observed case of fulminant liver failure:

The patient was diagnosed with MS and began treatment with daclizumab during the same month. The liver monitoring tests were performed in accordance with SmPC recommendations and were within the normal range 6 days prior to receiving the fourth/last dose of daclizumab. Twenty-five days after the last dose, the patient felt ill and experienced nausea and vomiting. Two days later the patient became severely jaundiced, and three days afterwards was diagnosed with acute liver failure. The patient underwent a liver transplant the next day, and died approximately one week later.

Notably, 2.5 weeks prior to initiation of daclizumab transaminase levels were elevated to ~2x ULN (ALT=84.8 U/l and AST 42.2 U/l). However, serum transaminase and bilirubin had returned to normal levels prior to initiating daclizumab. The patient was also taking concomitant medications including tizanidine (muscle relaxant, which also carries a risk of liver failure), an oral contraceptive, and vitamin D. In addition, the patient had a history of Hashimoto's thyroiditis.

Elevations of serum transaminases and serious hepatic injury have occurred in patients treated with daclizumab. Serious reactions, including autoimmune hepatitis, hepatitis and jaundice, have been observed in 1.7% of patients.

With this restriction of indication and the contraindication in patients with pre-existing hepatic disease or hepatic impairment, for some patients currently under treatment daclizumab may no longer be an appropriate treatment option. Physicians should re-evaluate promptly whether daclizumab is still the most appropriate MS therapy for each of your patients. Detailed information is included in the product information.

The EMA is further investigating the risk of liver injury associated to treatment with Zinbryta; any new advice will be communicated promptly.

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

It is easiest and quickest to report ADRs online via the Yellow Cards website - <https://yellowcard.mhra.gov.uk/>. 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 (biogen@professionalinformation.co.uk).

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

A handwritten signature in black ink that appears to read "Fiona Thomas".

Dr Fiona Thomas MBChB
Medical Director, UK and Ireland

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