NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission (EC):

Product name Procedure name	Zinbryta (daclizumab)
Active substance	daclizumab
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	Biogen Idec Ltd

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterised by inflammation, demyelination, and neuronal loss. The pathological changes underlying MS are believed to be mediated by activated, autoreactive lymphocytes which cross the blood-brain barrier (BBB) and initiate an immune-mediated cascade of events that injures both the grey and white matter of the brain. It is usually diagnosed between the ages of 20 to 40 years, with twice as many women affected as men.

Zinbryta (daclizumab) is a centrally authorised product approved in July 2016 for the treatment of adult patients with relapsing forms of multiple sclerosis. The recommended dose of daclizumab is 150 mg injected subcutaneously once a month. Daclizumab acts through a novel, reversible modulation of IL-2 signalling, inhibiting CD25- dependent, high-affinity IL-2 receptor signalling but leaving intermediate-affinity IL-2 receptor signalling intact. This signalling modulation results in several well-characterized immunologic changes that were hypothesized to result in selective targeting of both white and grey matter MS pathology while also preserving key protective functions of the immune system.

During the clinical development, serious hepatic adverse reactions, including autoimmune hepatitis, hepatitis and jaundice, were observed in 1% of patients and a case of fatal autoimmune hepatitis occurred in a patient re-initiating treatment with 300 mg of daclizumab after a planned 6 month treatment interruption period. Serum transaminase elevations occurred during treatment and up to 4 months after the last dose of daclizumab. Most patients had transaminase elevations that were asymptomatic and resolved spontaneously. Incidence of elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN) was reported in daclizumab-treated patients compared to placebo (4% versus <1%) or interferon beta-1a (intramuscular) (6% versus 3%). The incidence of discontinuation due to medicine related hepatic disorders was

5% in daclizumab-treated patients and 4% in interferon beta-1a (intramuscular).

In view of the above, transaminase elevations and serious hepatic injury were included as important identified risk in the risk management plan of Zinbryta (daclizumab) and consequently several risk minimisation measures were implemented in the form of a Patient Alert Card and a Hepatic Risk Management Guide to stress the need of monthly monitoring of liver function and the importance of an early identification of signs and symptoms, with specific recommendations on actions to be taken in case of signs of liver injury, such as discontinuation of treatment with daclizumab and potential consideration of additional therapy.

On 7 June 2017, the European Commission was informed of a fatal case of fulminant liver failure in a [redacted] patient treated with Zinbryta (daclizumab) in an ongoing observational study [redacted] The patient received a total of 4 doses of daclizumab. She underwent monthly liver function testing, as per recommendations in the product information. Five days prior to her last dose her liver functions tests were within normal limits. Approximately five weeks later she developed jaundice and a fulminant hepatic failure that required liver transplant after which she died.

In addition, in the 1st PSUR assessed by PRAC and covering the period from 27 May 2016 to 26 November 2016, 4 cases of serious liver injury were reported from clinical trials.

The seriousness of the reactions reported leading in one case to a fatal outcome, despite the monitoring of the patient's liver function being conducted as currently recommended in the product information, and the biological plausibility, warrant further investigation of this risk. Its impact on the benefit-risk balance of the medicinal product and the adequacy of the risk minimisation measures, with regard to liver toxicity, need to be assessed.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal product Zinbryta (daclizumab).

The EC requests the Agency to give its opinion as soon as possible and the latest by 30 November 2017 on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

In addition, the European Commission requests the Agency to give its opinion, as soon as possible, as to whether provisional measures are necessary to protect public health.

[redacted]

Signed

Date 09/06/2017

Olga Solomon
Head of Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General