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

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This notification is a referral under Article 20 of Regulation (EC) No 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 medicinal product approved in July 2016 for the treatment of adult patients with relapsing forms of multiple sclerosis. Under the Article 20 referral of Regulation (EC) No 726/2004 finalised on 8 January 2018 the use of daclizumab was limited to the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) who have had an inadequate response to at least two disease modifying therapies (DMTs) and for whom treatment with another DMT is contraindicated or otherwise unsuitable due to a risk of immune-mediated liver injury. The recommended dose of daclizumab is 150 mg injected subcutaneously once a month. Daclizumab acts through a reversible modulation of IL-2 signalling[1], inhibiting CD25- dependent[2], high-affinity IL-2 receptor signalling but leaving intermediate-affinity IL-2 receptor signalling intact. This signalling modulation results in several well-characterised 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.

The Paul-Ehrlich Institute (PEI) in Germany informed the regulatory network about 7 patients treated with daclizumab in 2016 and 2017 who have experienced after initiation of treatment serious immune-mediated adverse reactions in the CNS, including encephalitis and

[1] Interleukin-2
[2] Cell-dependent 25

encephalo-meningitis. Some of the cases were initially misinterpreted as worsening of the main disease (MS), but after the applied therapy in the form of corticosteroids and/or plasmapheresis did not improve the clinical situation, brain biopsies were obtained, showing inflammation characterised by the presence of multiple immunocompetent cell types, and in a few of the cases even of eosinophilic granulocytes, which is a finding uncharacteristic of the pathogenesis of MS. Several of these patients experienced fever, leukocytosis, exanthema/skin reactions of serious nature, which in combination of the findings of the biopsies may be interpreted as cases of drug reaction with eosinophilia and systemic symptoms (DRESS) with CNS involvement. The seriousness of the reactions, the clinical outcome reported, and the biological plausibility, were of serious concern to the PEI, as they suggest that treatment with daclizumab may lead in a number of patients to the development of immune-mediated CNS pathology with grave sequelae. Three additional cases have been reported worldwide.

In view of the seriousness of the newly available information and the biological plausibility, the risk of immune-mediated encephalitis and its impact on the benefit-risk balance of the medicinal product should be investigated, as well as the adequacy of the risk minimisation measures, with regard to immune-mediated CNS involvement (encephalitis), 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 31 July 2018 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 26.02.2018
Olga Solomon
Head of Medicines: policy, authorisation and monitoring
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