Annex I

Scientific conclusions

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Daclizumab beta is a humanised IgG1 monoclonal antibody that modulates IL-2 signalling by blocking CD25-dependent, high affinity IL-2 receptor signalling, resulting in higher levels of IL-2 available for signalling through the intermediate-affinity IL-2 receptor. Key effects of this IL-2 pathway modulation potentially related to the therapeutic effects of daclizumab beta in multiple sclerosis (MS) include selective antagonism of activated T-cell responses, and expansion of immunoregulatory $CD56^{bright}$ natural killer (NK) cells, which have been shown to selectively decrease activated T-cells. Together, these immunomodulatory effects of daclizumab beta are believed to reduce central nervous system (CNS) pathology in MS and thereby reduce the occurrence of relapses and disability progression.

Zinbryta (daclizumab beta) has been authorised in the European Union (EU) since 1 July 2016. As of November 2017, 2,251 patients had received Zinbryta in the clinical development program. The post-marketing exposure in the European Economic Area (EEA) is estimated at 3,290 patients (of which around 2,890 patients in Germany) and worldwide at 5,086 patients. In the European Union, as of 30 November 2017, daclizumab beta has been marketed in Austria, Belgium, Denmark, Finland, Germany, Ireland, Italy, Netherlands, Norway, Poland, Slovenia, Sweden and United Kingdom. It was initially indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS). A PRAC review concluded on 31 October 2017 (due to cases of immune-mediated liver injury) led to the restriction of indication to the treatment of adult patients with relapsing forms of multiple sclerosis 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. It is administered as 150 mg dose subcutaneously once a month.

On 20 February 2018, the Paul Ehrlich Institute (PEI) informed the EMA about five patients who were treated in 2016 and 2017 with daclizumab beta in Germany, and experienced worsening of disease after initiation of therapy. Administration of acute corticosteroids and/or plasmapheresis did not improve the clinical situation, brain biopsies were obtained, which showed an unexpected finding of massive inflammation with eosinophilic granulocytes (unexpected in MS patients). Four of the five patients experienced also fever, leukocytosis, exanthema/skin reactions, thus potentially meeting the criteria for DRESS. Further to that on 22 February, PEI informed about 2 new cases of immune-mediated disease with CNS involvement.

In view of the seriousness of the reactions reported 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 minimization measures with regard to immune-mediated CNS involvement (encephalitis) need to be assessed.

On 26 February 2018, pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Zinbryta should be maintained, varied, suspended or revoked. In addition, the European Commission requested the Agency to give its opinion, as soon as possible, as to whether provisional measures were necessary to protect public health

Overall summary of the scientific evaluation by the PRAC

Daclizumab beta is hypothesized to exert its activity in MS through immunomodulatory mechanisms. Immune-mediated or autoimmune conditions such as type I diabetes, colitis, autoimmune thyroiditis, pancreatitis, glomerulonephritis, among other, were reported in low numbers. Autoimmune haemolytic anemia is already known to be related to daclizumab beta treatment. It is plausible that the immunomodulatory effects of the drug are involved in immune-mediated adverse effects, such as

autoimmune hepatitis, and could be related to the reported cases of encephalitis and/or meningoencephalitis.

In the second PSUR (period from 27 November 2016 - 26 May 2017), the review of autoimmune encephalitis cases and other immune-related disorders cases showed that there was a wide variety of immune-mediated disorders reported (such as encompassed seronegative arthritis, blood dyscrasias, thyroid disorders, glomerulonephritis and skin and subcutaneous disorders). Although the absolute number of the individual reports for each disorder was low, cumulatively there were a significant number of autoimmune events possibly related to daclizumab beta treatment. More information concerning these immune-mediated events had been requested to the MAH to be submitted in the third PSUR. From the third PSUR (period from 27 May 2017 - 26 November 2017), there have also been some cases of unexpected deaths, attributed to cerebrovascular accidents, but with no detailed information on them that would conclusive allow for the exclusion of encephalitis.

Overall, 12 cases of encephalitis or encephalopathy in patients treated with daclizumab beta for multiple sclerosis have been identified. These cases concerned 10 females, 1 male (and 1 unknown), aged between 30 and 69 years-old; 9 cases occurred in Germany, 2 in USA and 1 in Spain. All cases were spontaneous reports, except for the Spanish case which came from an extension of a clinical trial. The number of doses received before the event was reported in all but two cases; it ranged between 1 and 8 doses, except for the Spanish patient who had received daclizumab beta for 4 years.

Some of these patients did not improve despite treatment with corticosteroids and/or plasmapheresis in these patients brain biopsies were obtained, which showed an unexpected finding of massive inflammation with eosinophilic granulocytes. At least 5 of these patients had clinical symptoms compatible with ‘drug rash with eosinophilia and systemic symptoms’ (DRESS) syndrome, one of which was confirmed with skin biopsy and one highly suspected.

Three of these cases had a fatal outcome, 2 cases are still intubated, 1 has an Expanded Disability Status Scale (EDSS) score 9.5, 1 recovered with sequelae, 1 partially recovered, and the remaining cases had an unknown outcome.

The PRAC discussed the possibility of the causal relationship of these adverse reactions, as well as the possible mechanism through which they could have been triggered. It was acknowledged that the mechanism of action of daclizumab beta is complex. Daclizumab beta binds to the alpha-subunit (CD25) of the high-affinity interleukin-2 (IL-2) receptor. Daclizumab beta blocks CD25 (alfa subunit of high affinity IL-2 receptor), decreasing the number and function of CD4+CD25+FoxP3+Treg and produces an activation and expansion of CD56 NK cells. This effect is probably mediated through excess of IL-2 produced by activated T cells that cannot bind to high affinity IL-2 receptors, but is available to bind to intermediate IL-2 receptors. Activation and expansion of NK cells may lead to a higher cytotoxic response that may be involved in the pathogenesis of autoimmune hepatitis and other autoimmune diseases. This is potentially a plausible mechanism which needs to be further investigated.

In summary, 12 cases of serious and potentially fatal immune-mediated events involving CNS, with symptoms initially compatible with relapse of MS and later on explained by unexpected findings in the neuropathology, with a predominantly inflammatory process and eosinophilic granulocytes, were reported. These cases are characterized by torpid progression and potentially fatal or disabling outcome. This adverse reaction appears unpredictable and no measure to minimize the risk has been identified at this stage.

Furthermore, the analysis of PSUR data indicated that a range of immune-mediated disorders were reported in other organs than the brain and liver following the use of Zinbryta. Whilst the absolute

numbers for each disorder is low, this raises concerns that these disorders could be induced by immune-mediated effects and could be causally associated with Zinbryta. .

It was noted that three Clinical studies are currently ongoing:

EXTEND: extension study to assess efficacy and safety in patients from the pivotal studies. It is ongoing in 9 countries with more than 400 patients. Due to the conclusion of the previous referral and based on the clinical characteristics of the patients, the MAH has already decided in January 2018 to stop this trial by 30 March 2018;

SUSTAIN: A phase 3b open label study to assess efficacy and safety of daclizumab beta in patients switching from natalizumab in 5 countries, 3 in EU (DE, IT and UK). There are no active patients;

ZEUS: non-interventional study in Germany with 609 patients enrolled currently. The MAH plans to terminate the study as a result of the product suspension in the EU.

PRAC has considered carefully the above described cases, the probable mechanism of action for these adverse events, along with the potential for auto-immune or immune-mediated reactions that appears associated with Zinbryta, the product mechanism of action, the biological plausibility, and that no risk minimisation measures (RMMs) can be foreseeable to prevent occurrence of these risks in patients on treatment with daclizumab beta at this stage. In light of all of the above and having carefully assessed all available data, PRAC considered at this stage that the benefit-risk balance of the product is no longer favourable and that urgent measures in accordance with Article 20(3) of Regulation (EC) No 726/2004, taking into account the grounds set out in Articles 116 and 117 of Directive 2001/83/EC, are needed to protect patients. The use and the marketing authorisation for Zinbryta should be suspended and the product should be recalled from the market at the level of pharmacies and hospitals.

In addition, no new patients should start treatment with Zinbryta. Healthcare professionals should contact patients currently being treated with Zinbryta and should stop their treatment and consider alternatives as a matter of urgency. Patients stopping treatment must be followed up for at least 6 months, as symptoms may appear after discontinuation of Zinbryta treatment.

The PRAC considered the alternative treatment options for the different stages or manifestations of the disease. Further, the PRAC took into consideration that interrupting treatment in patients whose disease is well-controlled with daclizumab beta may induce relapses, but considered that the serious risk of auto-immune or immune-mediated reactions outweighs the benefit that daclizumab beta may bring to relapsed patients eligible to the authorised indication.

It was noted that there are ongoing clinical studies for which the MAH informed PRAC that the treatment with daclizumab beta is to be stopped. National competent authorities competent for the regulatory oversight of these clinical studies should act accordingly.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Zinbryta, in particular the need for provisional measures in accordance with Article 20(3) of Regulation (EC) No 726/2004, taking into account the grounds set out in Articles 116 and 117 of Directive 2001/83/EC.
- The PRAC reviewed the totality of the available data, including data provided by the marketing authorisation holder in writing and in an oral explanation on the 12 cases of serious

encephalitis and meningo-encephalitis (of which three fatal) reported since the initial marketing authorisation and safety data from clinical trials, in relation to the overall risk of immune-mediated disorders with CNS involvement during treatment with Zinbryta. PRAC concluded that these adverse reactions could be causally associated with Zinbryta.

- In addition, PRAC also considered the known serious immune-mediated liver toxicity associated with Zinbryta as well as potential other immune-mediated disorders affecting other organs than the brain or the liver.
- In view of the above, the PRAC considered that the benefit-risk balance of Zinbryta is no longer favourable and that urgent measures are needed to protect patients.
- The PRAC recommended to suspend the use and the marketing authorisation for Zinbryta, and to recall all the batches of the medicinal product from the market up to the level of pharmacies and hospitals.
- Furthermore, PRAC recommended that a healthcare professional communication should be disseminated to inform healthcare professionals about the risks related to Zinbryta and provide instructions related to the cessation of the treatment and the follow-up of patients having received Zinbryta.