6 March 2018
EMA/159031/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report on provisional measures

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Zinbryta

INN/active substance: daclizumab beta

Procedure number: EMEA/H/A-20/1462/C/003862/0018

Note:

Assessment report as adopted by the PRAC with all information of a commercially confidential nature deleted.

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1. Information on the procedure

On 23 February 2018, the European Commission (EC) was informed on the cases of seven patients treated with daclizumab beta in 2016 and 2017 who have experienced after initiation of treatment serious immune-mediated adverse reactions in the central nervous system (CNS), including encephalitis and meningoencephalitis.

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.

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 regards 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

In parallel, the Marketing Authorisation Holder (MAH) of the product, informed the EC on the decision to voluntarily withdraw the marketing authorisation for Zinbryta (daclizumab beta) in the European Union.

2. Scientific discussion

2.1. Introduction

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) was authorised in the European Union (EU) on 1 July 2016. The post-marketing exposure in the European Economic Area (EEA) though 30 November 2017 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. The highest use of daclizumab beta in the EEA is in Germany.

Daclizumab beta was initially indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

In June 2017, a referral under the Article 20 of Regulation (EC) No 726/2004 was initiated to review the risk of liver injury, its impact on the benefit-risk balance of the medicinal product and the adequacy of the related risk minimisation measures (RMMs). This referral was triggered further to the report of a fatal case of fulminant liver failure in a patient treated with daclizumab beta in an ongoing observational study, despite monthly liver function testing performed in accordance with recommendations in the product information. In addition, four cases of serious liver injury were reported from clinical trials, in the context of the first periodic safety update report (PSUR). The PRAC review concluded on 31 October 2017 and 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.

The current review under Article 20 of Regulation (EC) No 726/2004 was initiated to assess the risk of immune-mediated diseases in the CNS. In February 2018, the German Medicines Authority Paul Ehrlich Institute (PEI) informed the regulatory network about seven patients treated with daclizumab beta in 2016 and 2017 who experienced serious immune-mediated adverse reactions in the CNS, including encephalitis and/or meningoencephalitis after initiation of treatment. Some of the cases were initially misinterpreted as worsening of the main disease (multiple sclerosis), but the clinical situation of the patients was not improved after therapy with corticosteroids and/or plasmapheresis. In order to further characterize the clinical outcome of these patients, brain biopsies were obtained, showing inflammation characterized by the presence of multiple immunocompetent cell types, and in a few of the cases even of eosinophilic granulocytes. This is an unexpected finding of the pathogenesis of MS. Several of these patients experienced fever, leukocytosis, exanthema/skin reactions of serious nature, which in combination with the findings of the biopsies may be interpreted as cases of drug reaction with eosinophilia and systemic symptoms (DRESS) with CNS involvement. In addition, two more cases from Germany and three more cases have been reported worldwide.

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).

On 1 March 2018, the MAH informed the Agency and the EC on their intention to voluntarily withdraw the marketing authorization in the EU and to terminate the ongoing clinical studies within the EU.

2.2. Data on safety

Case reports on immune-mediated disorders with CNS involvement

Twelve cases of encephalitis or encephalopathy in patients treated with daclizumab beta for multiple sclerosis has 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 are spontaneous reports, except the Spanish case which comes 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 the Spanish patient who had received daclizumab beta for 4 years.

Some of the cases were initially misinterpreted as worsening of the main disease (MS), but the clinical situation did not improve despite treatment with corticosteroids and/or plasmapheresis. In order to further characterize the clinical outcome of these patients, brain biopsies were obtained, showing inflammation characterized by the presence of multiple immunocompetent cell types, and in a few of the cases even of eosinophilic granulocytes. This is an unexpected finding of the pathogenesis of MS. 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, two cases are still intubated, one has an Expanded Disability Status Scale (EDSS) score 9.5, one recovered with sequelae, one partially recovered, and the remaining cases had an unknown outcome.

Description of cases

Case #1:

Female patient with secondary MS received only 2 doses of daclizumab beta starting in October 2016. Due to MS relapse the patient was treated with cortisone and plasmapheresis. An MRI performed in January revealed disease progression (acute MS relapse). In January, patient was treated with nitrofurantoin to an urinary tract infection (UTI). On February, after 5 cycles of plasmapheresis, patient was intubated presenting exanthema, body temperature 37.9 ºC and eosinophil count 0.83 (9.3%). In February, the performed brain biopsy showed acute inflammatory MS process with demyelinating lesions and inflammatory infiltrate (T-lymphocytes and B-lymphocytes as well as many plasma cells and eosinophil granulocytes). In March, eosinophil count was 1.91 (25.5%). The further brain biopsies that were performed showed presence of eosinophils. In October 2017, the final diagnosis of the patient's massive worsening of MS was DRESS syndrome due to daclizumab beta.

Case #2:

Female patient received 4 doses of daclizumab beta from October 2016 to January 2017. Previously the patient had received peginterferon β-1a from May to September 2016. The patient was hospitalised due to severe MS relapse from January 2017, receiving treatment with methylprednisolone. In March 2017 the patient experienced MS exacerbation and autoimmune encephalitis, anti-N-methyl-D-aspartic acid receptor (NMDAr) antibody encephalitis, while the liver values were increased. A cranial MRI showed exacerbation of MS with distinct progression in size of pre-existing MS lesions and multiple new lesions. Eosinophil count was 1.06 (11.4%) and body temperature was 39°C. A brain biopsy performed revealed inflammatory demyelinating CNS process with signs of early active demyelinating activity with evidence of macrophages and lymphocytes, numerous T-cells, plasma cells, and eosinophils. Cerebrospinal fluid (CSF) analysis revealed a positive presence of NMDAr antibodies and later the patient experienced exanthema over the whole body and pruritus. In October 2017 the diagnosis was DRESS syndrome and autoimmune encephalitis (anti-NMDAr encephalitis). Upon follow-up the neurologist clarified that DRESS was diagnosed due to the brain biopsy findings, the eosinophilia and the skin rash and noted that NMDAr encephalitis was comorbidity. The reporting neurologist assessed the causality of the event DRESS syndrome as related to daclizumab beta.

Case #3:

Female patient developed encephalitis 4.5 months after starting daclizumab beta and 1 month after the last dose of daclizumab beta. The patient received in total 2 doses of daclizumab beta from July 2017 to September 2017 and daclizumab beta was discontinued due to skin reactions. No MS therapy was administered for approximately 8 weeks following discontinuation of daclizumab beta. Following discontinuation, the patient was hospitalised presence of malaise, cough, fever, headaches, and joint pain. CSF revealed elevated white blood cells (WBC), protein and glucose levels. Follow-up MRI revealed overtly progressive cerebellar swelling most likely within the scope of cerebellitis. Hemicraniectomy and plasmapheresis were performed to address acute swelling and increased intracranial pressure. At the time of the report, the events were ongoing. Causality for the event of viral meningitis was assessed as being possibly related to daclizumab beta as neuropathological results showed pronounced inflammatory infiltrate including numerous eosinophilis infiltrating demyelinating lesions.

Case #4:

Male patient received only two doses of daclizumab beta (April, May 2017). Following this, the patient was admitted to the hospital and was diagnosed with “autoimmune-mediated encephalitis”. Treatment included immune-adsorption with intermittent administration of immunoglobulins and with cortisone therapy. In June 2017, a brain biopsy was performed and showed a highly active MS with a mixed inflammation infiltrate (T- and B-cells and myelin-phagocytizing macrophages). Acute disseminated encephalomyelitis was reported as recovered with sequelae. The report assessed causality as possibly related to daclizumab beta. The patient died in January 2018.

Case #5:

Female patient with Relapsing Remitting Multiple Sclerosis (RRMS) diagnosis, previously treated with betaferon (withdrawn due to skin reaction) received 8 doses of daclizumab beta from June 2017 to January 2018. The patient experienced life threatening lymphocytic meningoencephalitis (acute, aseptic), polyradiculitis with involvement of cranial nerves, nausea, headache and dysphagia. In December 2017, the patient experienced liquor pleocytosis, intensive care-dependent, required artificial ventilation, urinary incontinence and severe headache. According to data provided by the MAH, the patient is improving with rehabilitation.

Case #6:

Female patient with RRMS, previously treated with interferon beta-1a, and from April 2017 to November 2017 with daclizumab beta. The patient experienced MS exacerbation with more than 30 new lesions in MRI and potential DRESS. In November 2017, the patient had paraparesis, reduced vigilance, epileptic seizures, and recurrent fever. The report from neuropathologist informed microglia activation, encephalitic process with pronounced inflammatory infiltrate, predominantly consisting of cytotoxic T-cells. The patient experienced symptoms compatible with DRESS: eosinophilia in blood, generalized exanthema, fever, lymphadenopathy and swelling face. The patient was still intubated (23 February 2018) since November 2017.

Case #7:

Patient with massive MS relapse and with diagnosed of meningoencephalitis.

Case #8:

Female patient was administered daclizumab beta from November 2016 to September 2017. In August 2017, the patient experienced generalized weakness, nausea, and emesis. Brain MRI showed a lesion suspected as worsening MS. The patient was noted to be febrile; viral meningitis was a suspected diagnosis and the patient received intravenous acyclovir. A few days later the patient was hospitalised for potential MS flare and she experienced a generalized tonic-clonic seizure. Treatment included intravenous diazepam. The patient was intubated 4 days later due to respiratory failure secondary to seizure activity. MRI of the brain showed diffuse leptomeningeal enhancement and periventricular enhancing lesions consistent with demyelinating disease (MS), which was suggestive of active demyelination. A week later, brain biopsy showed benign brain tissue, no viral inclusions or malignant tissue, and NMDA antibodies were reported as detected in serum. The patient was treated empirically for an infectious process and MS exacerbation with no clinical improvement. The patient remained on the ventilator. Four days after that the patient was extubated and died later. The neurologist assessed causality as not related to daclizumab beta.

Case #9:

Female patient received daclizumab beta for Relapsing Remitting Sclerosis (RMS) and was hospitalised due to encephalitis. The reporting neurologist stated the patient had an immune disorder that caused the encephalitis. Information in diagnostic test results and treatment were not provided. The reported causality was not related. Daclizumab beta was discontinued and the outcome is unknown. No further details were provided.

Case #10:

Female patient received daclizumab beta from March 2017 to August 2017. Concurrent medical conditions included walking difficulty and demyelination. In October 2017, the patient was hospitalised due to aseptic meningoencephalitis. The patient initially presented with 5-day history of fever, confusion, and altered mental status. CSF analysis showed lymphocytosis with negative cultures. Treatment with intravenous methylprednisolone was initiated with clinical improvement. Patient was transferred to a rehabilitation centre and then discharged. At the time of the last follow up, the patient was reported as clinically stable. Daclizumab beta therapy had been already discontinued due to the lack of efficacy in August 2017. Causality was assessed as not related to daclizumab beta.

Case #11:

Female patient received her first dose of daclizumab beta in August 2013 as part of an ongoing clinical trial. In July 2017, approximately 4 years after the first dose of daclizumab beta, the patient experienced “acute confusional syndrome” and was hospitalised. CT scan showed extensive and severe defects that affected the frontal cortex, the anterior cingulate, temporal and bilateral parietal lobe, predominantly on the right. The subcortical structures had moderate hypoperfusion of the basal ganglia and bilateral thalamus; there were no findings on the cerebellum. Further CSF analyses showed questionable positive results for anti-N-methyl-D-aspartic acid receptor (NMDAr) antibody. After intravenous immunoglobulins treatment, the patient’s condition remained without symptomatic

remission, and was discharged with a diagnosis of changes in behaviour due to MS and possible autoimmune encephalitis. Around 15 days later, she was admitted to the intensive care unit for mechanical ventilation after empiric treatments with antibiotics, antivirals, and corticoids were started. Within 2 weeks indirect immunohistochemistry of the CSF was positive for anti-glutamate receptor, which confirmed the diagnosis of anti-NMDAr encephalitis in the context of a malignant neuroleptic syndrome. A week later, she was febrile, and an abdominal scan showed paralytic ileus and megacolon, which were assessed as probably related to anticholinergic treatment. Severe sepsis and peritonitis (potentially of urinary or abdominal origin) and oliguric renal failure were noted three days later. The subject was in a coma without sedation with Glasgow coma scale of 3 to 4, in spite of treatment with plasmapheresis (total 9 sessions). The patient had faecal peritonitis due to colonic ischemia and multiple perforations within a further week, and died a day later. The main cause of death was reported as septic shock with multi-organ failure due to faecal peritonitis secondary to multiple perforations in the colon. The neurologist reported that this was a complication of anti-NMDAr encephalitis with coma and with possible aetiologies occurring secondary to a chronic neurological disease, such as MS or possibly, the origin of an autoimmune disease, such as lupus.

Case #12:

This case was reported on 20 February 2018. A neurologist reported to the MAH a case of “eosinophilic meningeasis, suspicion of DRESS” in a patient under daclizumab beta treatment.

Clinical studies

During clinical trials, immune-mediated or autoimmune conditions such as type I diabetes, colitis, autoimmune thyroiditis, pancreatitis, glomerulonephritis, among other, were reported in low numbers. Autoimmune haemolytic anaemia is already known to be related to daclizumab beta treatment. Although daclizumab beta is recognized for its immunosuppressant activity, immune-mediated or auto-immune adverse events were not found to be significant in clinical trials. However, the referral procedure conducted in 2017 concerned immune-mediated hepatitis and therefore a link with the mechanism involved in the cases that triggered the current referral is possible.

No signal on encephalitis has been raised during clinical trials; however these adverse reactions could be causally associated with Zinbryta. PRAC considered that during clinical trials cases of encephalitis and encephalo-meningitis may have been misclassified as worsening of the main disease (MS). This is in line with the encephalitis cases assessed in this referral, which were initially misinterpreted as worsening of the main disease (MS).

It was noted that three clinical studies are currently ongoing:

The EXTEND study is the extension study to assess efficacy and safety in patients from the pivotal studies. It is ongoing in 9 countries with more than 400 participants. 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 prematurely terminate this trial by 30 March 2018.

The SUSTAIN study is a phase 3b open label study to assess efficacy and safety of daclizumab beta in patients switching from natalizumab. It is ongoing in 5 countries, 3 in EU (Germany, Italy and UK). The study is being closed. Enrolled subjects are discontinuing treatment with daclizumab and no new patients will be enrolled. Subjects enrolled in the EU will not receive any further doses.

The ZEUS study is a non-interventional study in Germany with 609 patients enrolled currently. The study will be terminated as a result of the product suspension in EU.

Data from PSURs

The review of autoimmune encephalitis cases and other immune-related disorders cases in the second PSUR covering the period 27 November 2016 to 26 May 2017, showed that there is 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 is low, cumulatively there is high number of autoimmune events possibly related to daclizumab beta treatment. More information concerning these immune-mediated events had been requested to the MAH for submission in the third PSUR. Since the third PSUR (period 27 May 2017 to 26 November 2017), there have also been some cases of unexpected deaths, attributed to cerebrovascular accidents but with no detailed information allowing the exclusion of encephalitis.

Immune-mediated liver toxicity

During the previous referral, the PRAC assessed a fatal case of fulminant liver failure and four cases of serious liver injury that occurred since the marketing authorisation, in the context of the data generated during the clinical development of daclizumab beta. Transaminases elevations and serious hepatic injury are known risks associated to treatment with daclizumab beta but the RMMs implemented, in particular the monthly liver testing, have not been effective to prevent the fatal case of fulminant hepatic failure.

During the clinical development, transaminases elevations and serious hepatic injury were identified as important identified risks. The majority of findings were asymptomatic transaminases elevations. In the clinical development program, the incidence of hepatic AEs (identified using the drug-related hepatic disorders standardized MedDRA query) was 16%. Severe events occurred in 2% and serious hepatic events occurred in 1% of patients treated with daclizumab beta.

Based on the review of the cases, liver injuries caused by daclizumab beta were not dose-dependent and occurred throughout treatment and up to 6 months after treatment. No time window of a higher risk was identified. Although the exact physiopathological mechanism for the development of serious liver injury is unknown, the characteristics were highly suggestive of an immune-mediated mechanism and the role of prior history of immune disorders or potential consequences on the development of other autoimmune disorders are unknown. It was further noted that at least two serious cases of liver injury occurred in patients with pre-existing autoimmune conditions other than MS.

In the previous referral, the PRAC concluded that daclizumab beta is associated with a potentially fatal risk of immune-mediated liver injury and the occurrence of daclizumab beta induced liver injury is considered to be unpredictable. Therefore the PRAC recommended that Zinbryta use should be contraindicated in patients with pre-existing hepatic disease or hepatic impairment.

2.3. Conclusion on safety

In summary, 12 cases of serious and potentially fatal immune-mediated events involving CNS, with symptoms initially compatible with relapse of MS and then later on explained by unexpected findings in the neuropathology. These cases are characterized by torpid progression and potentially fatal or disabling outcome. The assessment revealed a likely causality between these cases and daclizumab beta use.

This adverse reaction appears unpredictable and no measure to minimize the risk has been identified. The immunomodulatory effects are involved in immune-mediated adverse effects, such as autoimmune hepatitis, and it could be related to the cases of encephalitis and/or meningoencephalitis.

Furthermore, the analysis of PSUR data indicated that a range of immune-mediated disorders were reported following the use of Zinbryta in other organs than the brain and liver (such as encompassed seronegative arthritis, blood dyscrasias, thyroid disorders, glomerulonephritis and skin and subcutaneous disorders). 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. The above, in addition to the known immune-mediated liver toxicity raises serious concerns on the risks related to the use of Zinbryta.

3. Benefit-risk balance

Daclizumab beta is a humanized IgG1 monoclonal antibody that binds to CD25 (IL-2Rα), and prevents IL-2 binding to CD25. Daclizumab beta modulates IL-2 signaling by blocking CD25-dependent, high-affinity IL-2 receptor signaling, resulting in higher levels of IL-2 available for signaling 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 MS include selective antagonism of activated T-cell responses, and expansion of immunoregulatory CD56bright 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 CNS pathology in MS and thereby reduce the occurrence of relapses and disability progression.

The referral procedure conducted in 2017 concerned immune-mediated hepatitis and a link with the mechanism involved in the cases that triggered the current referral is possible.

During clinical trials, immune-mediated or autoimmune conditions such as type I diabetes, colitis, autoimmune thyroiditis, pancreatitis, glomerulonephritis, among other, were reported in low numbers. Autoimmune haemolytic anaemia is already known to be related to daclizumab beta treatment. The immunomodulatory effects are involved in immune-mediated adverse effects, such as autoimmune hepatitis (trigger of previous referrals), and it could be related to the cases of encephalitis and/or meningoencephalitis.

During the assessment of the second PSUR (27 November 2016 to 26 May 2017), a wide variety of immune mediated disorders were identified with at least a reasonable possibility of relatedness affecting different organs. Most of them are single cases but taking together all these cases there is a high number of autoimmune events possibly related to daclizumab beta treatment. Those immune mediated adverse events encompassed seronegative arthritis, blood dyscrasias, thyroid disorders, glomerulonephritis and skin and subcutaneous disorders.

On 1 March 2018, the MAH informed the Agency and the EC on their intention to voluntarily withdraw the marketing authorization in the EU and to terminate the ongoing clinical studies within the EU. Based logistical and clinical grounds, the MAH proposed to withdraw the product from the European market as soon as possible and a maximum timeframe of 90 days. In view of the seriousness of the reactions, clinical outcome reported and biological plausibility, PRAC considered that this timeframe was unacceptable and urged the need for provisional measures including suspension of both the marketing authorization and supply of the medicinal product with immediate effect.

Therefore, while the magnitude and nature of the risks are being reviewed in depth, considering the biological plausibility, the seriousness of the cases of CNS autoimmunity process with fatal/serious

outcomes along with the potential for auto-immune or immune-mediated reactions that appears associated with Zinbryta, the product mechanism of action, and that no effective RMM can be foreseeable to prevent occurrence of these risks in patients on treatment with daclizumab beta at this stage, the PRAC considered that the benefit-risk balance of Zinbryta 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, should stop their treatment and consider alternatives. 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 informs 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.

4. Direct Healthcare Professional Communication / Communication plan

The PRAC adopted the content of a Direct Healthcare Professional Communication (DHPC) to inform HCPs of the suspension of use for Zinbryta (daclizumab beta), of the cases of encephalitis and meningo-encephalitis and to provide instructions related to the cessation of the treatment and the follow-up of patients having received Zinbryta. The PRAC also agreed on a communication plan.

5. Provisional measures

Given the new identified risks, and the fact that no risk minimisation measures are considered adequate to address these concerns, the Committee considers that provisional measures are needed and recommends 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.

6. Grounds for 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.