17 May 2018
EMA/377140/2018
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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 and considered by the CHMP 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.

On 6 March 2018, the PRAC adopted provisional measures, as the Committee considered that the benefit-risk balance of Zinbryta was 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, were needed to protect patients.

The use and the marketing authorisation for Zinbryta was suspended and the product was recalled from the market at the level of pharmacies and hospitals, 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, while the magnitude and nature of the risks were being reviewed in depth.

2. Scientific discussion

2.1. Introduction

Daclizumab beta is a humanized immunoglobulin G (IgG) 1 monoclonal antibody that binds to CD25 and prevents IL-2 binding to CD25. Daclizumab 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 in multiple sclerosis include selective antagonism of activated T-cell responses and expansion of immunoregulatory CD56 bright natural killer

cells, which have been shown to selectively decrease activated T cells. These immunomodulatory effects of daclizumab are believed to reduce central nervous system pathology in multiple sclerosis and thereby reduce the occurrence of relapses and disability progression.

Daclizumab beta was initially indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS). It is administered as 150 mg dose subcutaneously once a month.

In June 2017, a referral (EMEA/H/A-20/1456/C/003862/0010) 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). It 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.

The current referral (EMEA/H/A-20/1462/C/003862/0018) was triggered based on cases of inflammatory brain disorders. After a preliminary review of these cases, the PRAC recommended via provisional measures on 2 March 2018 the immediate suspension of the use of the product and its marketing authorisation, together with a recall of available batches at the level of pharmacies and hospitals. The European Commission adopted a Commission Decision based on this recommendation on 8 March 2018.

As of 26 November 2017, daclizumab has been authorised in a total of 35 countries worldwide, including the US, Australia, Canada, Switzerland, and countries within the European Economic Area (EEA).

Zinbryta is available as a single-dose pre-filled syringe (PFS) or pre-filled pen (PFP) providing 150 mg of daclizumab beta in 1 mL of solution. The recommended dosage is 150 mg injected subcutaneously once a month.

2.2. Clinical aspects

2.2.1. Efficacy

Data on efficacy

The efficacy of daclizumab was demonstrated in two pivotal studies in subjects with relapsing-remitting multiple sclerosis (RRMS), which led to the authorised indication in relapsing multiple sclerosis. The two studies are briefly presented here as their safety data are taken into account during this review. There were no new efficacy data that were made available during this assessment.

Study 205MS201 was a placebo-controlled study, and study 205MS301 an active-controlled study versus interferon beta-1a (IFN β-1a). Both trials enrolled a range of RRMS subjects who had recent relapse activity and were representative of the broader population of patients with RMS. Both studies demonstrated an effect of daclizumab on the primary efficacy endpoint of the annualized relapse rate: a 54% reduction versus placebo in Study 201 and a 45% reduction versus IFN β-1a in Study 301 ($p < 0.0001$ for both). The risk of relapse was reduced by 55% over 1 year in daclizumab versus placebo-

treated subjects in Study 201 (p <0.0001) and by 39% over 1 year and by 41% over 2 to 3 years in daclizumab versus IFN β-1a-treated subjects in Study 301 (p <0.0001 for both).

The MAH, Biogen, has made a subgroup analysis in both studies for patients with highly active disease and patient with non-highly active disease, for the following endpoints by baseline disease activity level: annualized relapse rate (using independent neurology evaluation committee (INEC) confirmed relapses), number of new or newly enlarging T2 lesions and 6-month sustained disability progression.

Patients with highly active disease have been defined by the MAH for these analyses as: (1) Subjects with 2 or more relapses in 1 year, and with 1 or more Gadolinium (Gd)-enhancing lesions on brain magnetic resonance imaging (MRI) or (2) Subjects who failed to respond to a full and adequate course (at least 1 year of treatment) of any DMT or specifically IFN-β, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years. The MAH has provided three different analyses: failure to a full and adequate course of IFN β or any DMT and a third analysis in rapidly evolving severe disease, combining the previous population.

Results from the placebo controlled study (205MS201) are limited by the small sample size and the relatively small proportion of subjects with highly active disease (around 20%, corresponding to 121 out of 600). The study 205MS301 which had duration of 2 to 3 years provides data of approximately 40% of patients with highly active disease (744 out of 1841).

2.2.2. Safety

During the adoption by PRAC of the provisional measures in March 2018, part of the data was assessed, due to the emergent character at that time.

In this assessment all relevant data, including the cases seen in the provisional measures are presented and discussed, in order to have the overall scientific view based on the overall evidence.

Overview of exposure data

Daclizumab beta has been administered to 10,503 patients worldwide since product launch, representing a total of 13,163 patient-years of exposure. The MAH, Biogen, has sponsored 7 interventional Phase 2 or Phase 3 studies of daclizumab in subjects with relapsing multiple sclerosis (RMS). Based on the data available as of 12 March 2018, 2,266 subjects have received treatment in these 7 clinical studies, representing approximately 9,017 patient-years of exposure. Specifically, in the European Union (EU), 1,290 subjects have received daclizumab in a clinical study, representing 5,340 patient-years of exposure.

Regarding postmarketing exposure (including the Biogen-sponsored non-interventional study ZEUS), data are available through to 31 January 2018. Across all countries where daclizumab has been marketed, approximately 8,237 patients have received daclizumab, representing an estimated 4,146 patient-years of exposure. Among the Member States of the European Union and the European Economic Area where daclizumab beta has been launched, approximately 5,469 patients have been exposed, representing 2,833 patient-years of exposure. Study GER-ZIN-17-11131 was a non-Biogen-sponsored study conducted at the Department of Neurology, University of Münster (Germany) and aimed at evaluating changes in the immune-cell profile of RMS patients during treatment; 15 patients were enrolled before study closure upon suspension of Zinbryta's marketing authorization in the EU.

Germany is the country with the highest exposure in the EU.

Data on safety

A. Cases of auto-immune disorders with CNS involvement

i. Clinical trials

A total of 2,266 subjects received daclizumab in clinical trials, representing 9,107 patient-years. Two cases were retrieved following search. The summary narratives of the two cases are as follows:

Case #1:

This case (from 205-MS-202; SELECT study) concerns a 27 year-old male from Germany. The patient received the first dose of blinded study medication in March 2011 and the second one in April 2011. Five days later he developed a rash. He was aggressive and seemed to have mild trouble concentrating. The physical examimation was normal except for a maculo-papular rash. The magnetic resonance imaging (MRI) showed multiple brain Gd-enhancing lesions. Cerebrospinal fluid (CSF) analysis showed 309 cells/µl, three erythrocytes and 1080 protein mg/l. The dermatological assessment confirmed maculo-papular rash. About five weeks after the start of study medication, the subject was hospitalised. Treatment included IV aciclovir, ampicillin, and ciprofloxacin. A cranial magnetic resonance imaging (MRI) revealed that in comparison with the previous examination, several intraparenchymal lesions were either new or progressing in size. The neuropsychological deficits, the tremor of the hands, and the skin rash improved and finally completely remitted. The subject was discharged. Upon a follow-up visit one week after the discharge, the subject was well, without neuropsychological deficits and skin rash, and minimal tremor of the left hand. EDSS upon follow-up was 2.5, unchanged from the status before admission to hospital. Lab results were unremarkable, bone marrow biopsy, CT chest and abdomen, peripheral neurography, ophthalmology, EEG, and Doppler scan were normal. PCR for adenovirus, CMV, EBV, JCV, BK virus, Adeno-Associated Satellite Virus, Picornavirus, Rubella, and Toxoplasma were all also unremarkable. According to the investigator, the following lab results were of note: IgE 1234 U/ml, leukocytes initially 309 U/ml down to 48 U/ml upon discharge, protein 1195 mg/l down to 580 mg/l upon discharge. Contrast MRI showed periventricular lesions and very prominent Virchow-Robin spaces with contrast enhancement. According to the investigator, these were compatible with MS, but lymphoma could not be ruled out. Spectroscopy of a left frontal lesion revealed choline increase and N-acetylaspartate (NAA) reduction. The investigator updated the event term to "Aseptic meningitis."

According to the diagnostic criteria for encephalitis personality change is a major criteria for the diagnosis and the patient is reported to be aggressive and mild trouble concentrating. Taking into account that all causes of meningitis were excluded and due to the temporal sequence of the events, the PRAC considered that the role of daclizumab in this case is plausible.

Case #2:

This case (from study 205-MS-303) describes a 38 year-old female from Spain with medical history of bipolar disorder, paralytic ileus and megacolon. The patient received daclizumab from Aug 2013 to Jun 2017. In April 2017, the patient presented to the emergency department with aphasia; a brain MRI was thought to be compatible with MS relapse. The patient experienced episodes of aphasia for approximately 1 month and a half. In July 2017, aphasia worsened, and the patient was admitted to the hospital two days after. The patient was noted to exhibit aggressive and agitated behavior, with repetitive and incoherent speech. During this hospitalization, CSF analysis was reported as normal,

with the exception of detection of NMDAr antibodies. On two occasions, the NMDAr antibody test in the CSF was reported to be positive. In August 2017, the patient was admitted with disorganized thought and uninhibited behavior. Within the first 2 days of hospitalization, the patient had fever up to 39°C and headaches. Brain computed tomography (CT) showed no relevant findings. CSF testing results included: leukocytes 79 (reference range 0 to 5), polymorphonuclear leukocytes (PMN) 0%, lymphocytes 100%; glucose 53; protein 37 (units not provided). Suspected diagnosis included viral meningitis/encephalitis with possible NMDAr encephalitis due to the detection of anti-NMDAr antibodies. Empiric antibiotics, antivirals, and corticoid treatment were initiated. Anti-NMDA testing was positive and plasmapheresis was initiated. The patient experienced fever with chills. Urine culture was positive for *Streptococcus agalactiae*, and the patient was treated with ampicillin. Brain MRI showed lesions compatible with autoinmune encephalitis. A week later the subject deteriorated and was found unconscious with high fever, rigid abdomen, and absent bowel sounds. Severe sepsis of abdominal and/or urinary origin was diagnosed. The following week the subject was in a coma without sedation despite treatment with plasmapheresis. Treatment with rituximab and cyclophosphamide was initiated. Urgent surgical intervention was undertaken due to the acute abdomen with fecal peritonitis secondary to colonic ischemia and multiple perforations. The investigator clarified that the event "septic shock due to a perforated and ischemic colon" started on 24 September 2017. The neurologist considered the events not related to daclizumab beta.

Although this case is compatible with autoimmune encephalitis related to NMDAr, the long time to onset is not similar to the pattern of autoimmune encephalitis which triggered this review.

ii. Post-marketing

From post-marketing sources, a total of 1,607 cases were identified with at least 1 CNS ADR as of 01 March 2018. Of these cases, 156 serious CNS ADRs were reported in 129 cases. Criteria used to select these cases were not provided. A summary is as follows: there are 129 cases reporting serious SNC ADRs with age ranging from 22 to 79 years (median 45,3 years; 26 unknown); 98 of them were female (76%), 27 male (21%) and in 4 gender was unknown (3%); most of the cases come from USA: 87 (67%), 33 comes from DE (26%), 4 from Australia (3%), 3 from Puerto Rico (2%) and 1 each from the Netherlands and Switzerland (1%). 83 cases were received from solicited sources, 41 from spontaneous reports and 5 from the non-interventional study EUR-ZIN-16-11024 (ZEUS) in Germany.

Nine (9) cases were identified in which the description suggest potential encephalitis or meningoencephalitis and the causality of daclizumab could not be ruled out. With these criteria, the summary of the cases is as follows:

Case #1:

This spontaneous post-marketing case concerns a 43 year-old female from Germany with diagnosis of RRMS. She received daclizumab from Oct 2016 to Nov 2016. The patient experienced severe decompensation of her CNS and required hospitalization. Due to the unexplained and intractable worsening of her condition, the patient underwent a brain biopsy indicating a primarily inflammatory process with T and B lymphocytes and plasma cells and unexpected finding of eosinophils in the sample; the symptoms were attributed to a severe MS relapse, and the patient was treated with high doses of corticosteroids and plasmapheresis; daclizumab treatment was discontinued. The set of symptoms comprised severe MS relapse, fever, rash, pathological finding in laboratory values, and findings in biopsy corresponding to the diagnostic criteria of DRESS assessed as related to daclizumab by the neurologist. There were no indications of an infectious disease (JCV), primary vasculitis or

lymphoma. The patient had extremely severe disabilities (tetraplegia and involvement of multiple cranial nerves with a tracheal cannula for respiratory support) and required permanent nursing.

This case describes a clinical picture of a severe MS relapse with atypical findings in the brain biopsy such as eosinophilic granulocytes after two doses of daclizumab and severe sequalae. Infectious diseases (including JCV), vasculitis or lymphoma were ruled out. The analysis of this patient in the context of patients with similar characteristics points out an excessive immune-related CNS reaction attributable to daclizumab.

Case #2:

This spontaneous post-marketing case from Germany concerns a 30 year-old female who received daclizumab beta for RRMS from Oct 2016 to Jan 2017. The patient was hospitalised due to massive worsening of the basic disease MS and was treated with high dose steroid therapy and daclizumab was discontinued. Autoimmune encephalitis was suspected and a brain biopsy was obtained with the unexpected finding of eosinophils in the sample. The set of symptoms comprising severe MS relapse, fever, rash, lymph nodes swollen in the cervical and nuchal regions, pathological findings in lab values and findings in biopsy corresponded to the diagnostic criteria of DRESS and autoimmune encephalitis (NMDA antibody positive). Ovarian tumour was excluded.

This patient experienced a complex picture of severe MS relapse unwarranted to lack of efficacy of daclizumab, with epileptic seizures, symptoms of DRESS, disabling / incapacitating symptoms and with no indication of PML or neuromyelitis disorder. The diagnosis was provided as inflammatory demyelinating CNS process in the line with other patients with similar characteristics.

Case #3:

This case from Germany involved a 51-year old male patient who received 2 doses of daclizumab from Apr 2017 to May 2017. In Oct 2016, bilateral glioma of the optic nerve (WHO stage II-III) was found and was treated with proton beam therapy in Feb 2017. The patient was hospitalized for approximately 86 days from May 2017 to Aug 2017 due to massive disease exacerbation of known MS activated. Biopsy of a lesion left at the anterior horn of the lateral ventricle did not show evidence of lymphoma, other malignant lesions or PML. Biopsy histology indicated a primarily inflammatory process with T and B lymphocytes and remarkable many plasma cells. He was diagnosed with autoimmune encephalitis. As leading differential diagnosis, the neurologists assumed a severe and complex immunological interaction in the presence of administered daclizumab therapy and in parallel optic glioma, resulting in a fulminant aggravation of the pre-existing MS disease by initiation of tumor-specific NK cells and a secondary auto inflammatory amplification of the basic auto-immunological process of the MS disease. The patient died due to respiratory arrest in mid-Jan 2018. According to the neurologist, the analysis of the clinical data as a whole with six other patients revealed a largely consistent picture: an excessive immune-mediated CNS reaction caused by daclizumab treatment.

This case is confounded by the medical history of glioma of the optic nerve and the proton beam therapy; however, the worsening of the MS after two doses of daclizumab, the findings of the biopsy and the context of patients with similar characteristics support the role of daclizumab in the acute disseminated encephalomyelitis experienced by this patient.

Case #4:

This case involves a 69 year old female from USA who received daclizumab from Feb 2017 to Aug 2017. The patient was hospitalised for five days from Oct 2017 due to aseptic meningoencephalitis. The patient experienced lack of efficacy, five-day history of fever, confusion and altered mental status. CSF examination showed lymphocytosis with negative cultures. The outcome of the event and whether daclizumab treatment continues is unknown.

Scarce information is provided in this case; however, taken into account the clinical picture of the patient and the characteristics of cases under review, causality of daclizumab cannot be ruled out.

Case #5:

This solicited case from USA involves a 60-year old female who received daclizumab from Nov 2016 to Sep 17. The patient was hospitalised in Sep 2017 due to disorientation, change of mental status, hallucinations, seizures, and spinal fluid with elevated protein and WBC. She was found to have encephalitis of unknown aetiology with ultra refractory seizures/ultra refractory status epilepticus. A brain biopsy was performed in Sep 2017 ruling out virus infections and lymphoma. White matter with macrophage and T lymphocyte infiltrate and gliosis was found. By the end of Sept 2017, the patient was in a medically induced coma, was extubated and later died.

Taking into account the clinical picture of the patient, the findings of the brain biopsy and in the context of the number of cases with similar characteristics, the role of daclizumab is likely.

Case #6:

This spontaneous post marketing case from Germany involves a 33 year old female treated with daclizumab from Jul 2017 to Sept 2017 who presented with marked malaise, fatigue, cough, fever and joint pain for approximately three to four days, holocephalic headache and was admitted to the hospital on 24 Oct 2017. CSF diagnostics revealed pleocytosis with 616/3 WBC, elevated total protein in CSF and decreased glucose. Antibiotic and antiviral therapy was started with no improvement. Immediate MRI imaging was performed to rule out PML revealing marked disseminated demyelinating lesions in the presence of known MS, primarily in the supratentorial region, also isolated in the infratentorial region in the cerebellar peduncles, in the subcortical white matter as well as in the upper cervical spinal cord (no consistent with PML). Due to the unexplained and intractable worsening of her condition, the patient underwent a brain biopsy, leading to right frontal, parenchymal bleeding. The result of brain biopsy showed proof of eosinophil granulocytes meningeal and vascular. Abundant eosinophilic granulocytes visible are atypical for classic MS lesions. Pathogens were subsequently ruled out. The patient was diagnosed with rhombencephalitis/meningo-myeloencephalitis and DRESS-like syndrome (onset unknown). The patient also developed massive swelling on the brain as part of the inflammatory process, resulting in herniation of the brain as a result of increased intracranial pressure, requiring a craniotomy with ventricular drainage for external pressure relief. The alterations were attributed to daclizumab treatment by the physician as similar cases had been seen before. The patient has extremely severe disabilities and requires permanent nursing.

Analysis of the patient's clinical data in conjunction with that of six other patients yielded a consistent picture of an excessive immune-related CNS reaction caused by daclizumab treatment. The major infiltration with eosinophilic granulocytes is striking.

Case #7:

This spontaneous post marketing case from Australia concerns a 34 year-old male who initiated daclizumab treatment in March 2017 and after 8 doses experienced a dreadful headaches, some tingling down his right arm and leg as well as his right lower leg was slow or "dull" and not working as quickly. Based on MRI findings and previous treatment with natalizumab, PML was suspected and brain biopsy was performed. Brain biopsy results looked like demyelination and PML was ruled out. According to the physician, since becoming aware of the latest information he now has encephalitis (onset unknown) as a possible diagnosis for this patient. Daclizumab treatment was permanently discontinued.

In the light of the cases reported of immune-related CNS reactions caused by daclizumab, the role of daclizumab is likely.

Case #8:

This spontaneous post marketing case from Switzerland reported by a neurologist involved a 41 year old female who received one dose of daclizumab on Apr-2017. A week later the patient experienced severe progressive neurological deterioration with quadrant anopsy on the bottom right, hemiplegia right, aphasia, dysphagia, and vigilance disturbance leading to suspicion of neuromyelitis optica spectrum disorders. Stereotactic biopsy was performed showing no evidence of PML or neoplasm and with demyelination and inflammation with severe damage of astrocytes. The event was temporally related to daclizumab and treatment was permanently discontinued. The event resolved with sequelae in Feb 2018.

Due to the biopsy findings, the temporal sequence of the events, and the ruling out of alternatives causes, association to daclizumab is likely.

Case #9:

This case concerns a 33 year old female from Germany treated with daclizumab from Jun-2017 to Dec-2017. She experienced headache, arthralgia, back pain, signs of polyradiculitis and increasing tetraparesis and was admitted to hospital 08 Jan 2018 due to life threatening meningoencephalitis described as acute lymphocytic, aseptic meningoencephalitis and polyradiculitis with involvement of cranial nerves (onset Dec 2017). Clinical symptoms included worsening of general condition, nausea, massive vomiting, numbness and swelling of lips, joint pain, diffuse feeling of dizziness and headache. CSF analysis on 10-Jan-2018 revealed increased cell count of 62 Mpt/l and protein to 200. Treatment with corticosteroids, antibiotics and antivirals were initiated. Clinical deterioration continued with symptoms of dysarthria, dysphagia, facial paresis, ophthalmoplegia, respiratory insufficiency, and high-grade pareses requiring intermittent artificial ventilation while in ICU. Meningoencephalitis was suspected as a diagnosis of exclusion; and causality was assessed by neurologist as possibly related to daclizumab. Complete virological and microbiological diagnostic investigations were negative. Systemic causes as oncologic diseases, lupus, vasculitis were excluded. Analysis of clinical data in comparison with six other patients revealed a largely consistent picture on the whole: an excessive immune-mediated CNS reaction caused by daclizumab. Patient was discharged on 01 Mar 2018 in a stabilized and improved clinical condition but with still significant residual symptoms (flaccid tetraparesis, dysphagia, tracheostoma care) into a rehabilitation facility.

The clinical picture and the sequence of the events resemble the other cases described and related to daclizumab.

In addition to the nine cases above, four extra cases were identified with diagnoses of coma, encephalitis, aseptic meningitis and eosinophile meningeasis with insufficient information to assess causality. The summary of these four cases is as follows:

Cases #10-13:

- Solicited post-marketing case, not-medically confirmed, in a 56 year old female who experienced being comatose. Daclizumab treatment was discontinued; dates, events and other relevant information are unknown.
- Female in treatment with daclizumab who was hospitalized due to encephalitis. The outcome is unknown and the action with daclizumab treatment is unknown. No further details are provided.
- A spontaneous post marketing report from USA communicated by a physician, involving an adult patient who developed aseptic meningitis. Causality was assessed as related by the reporter. No further information is available
- This case from Germany concerns an adult female patient who received four doses of daclizumab and experienced DRESS syndrome (meningo-cerebral) characterized by pustular rash on the belly and eosinophile meningeasis.

These four cases provide insufficient information to characterise the event and to further assess causality with daclizumab, therefore, these cases are not accounted in the conclusion.

All the above immune-mediated adverse events involving the central nervous system that have been identified share the same clinical picture including more severe than expected relapse of multiple sclerosis, resistant to treatment with corticosteroids and/or plasmapheresis, unexpected findings in the brain biopsies when performed and devastating or fatal outcome in most of the cases. Of note, some of these patients also experienced some symptoms of DRESS syndrome. Although the specific physiopathological mechanism by which daclizumab cause immune-mediated disorder involving CNS remains unknown, it is proved that daclizumab trigger immune-mediated events such as hepatitis or autoimmune haemolytic anaemia, among others.

B. Cases related to lack of efficacy

Cases of lack of efficacy might have been misclassified; such cases from clinical trials as well from post-marketing experience were again reviewed.

i. Clinical trials

630 serious events were identified after having performed a search with the SMQ of lack of efficacy plus additional PTs of MS and MS relapse with any causality. Cases in which the product was discontinued were selected for a further review. Then, cases with torpid evolution, more serious than expected MS relapse or refractory to standard clinical care were reviewed. A summary of these cases is presented here.

Case #1

A fatal case concerns a 46 year old female from India, who started treatment in March 2011 and in June 2011 developed progressive difficulties in walking, altered sensorium for 15 days and fever for 5 days. The MRI showed increased white matter lesions extensive and bilateral and increased cerebral demyelination. The investigator added the event "Demylinating Disease of Brain". The patient was in bed unable to walk, she developed an infected bed sore and recurrent aspiration pneumonia, followed

Case #2

A fatal case involves a 37 year old female from France who received 3 doses of daclizumab and developed a severe MS relapse. The patient was hospitalized due to exacerbation of multiple sclerosis of a tetraparesis type. The brain MRI scan showed numerous white matter and subtentorial lesions and lesions in the medulla as well. An MRI was >20 gadolinium enhancement new lesions and the patient was treated with methylprednisolone followed by 6 plasmapharesis treatments. Expanded disability status score (EDSS) increased to 9. Since this relapse, she was hospitalised in the Intensive Care Department. The subject's neurological symptoms improved initially but then the patient was re-hospitalised because of an occlusion of the small intestine confirmed by an abdomino-pelvic scan. The physician confirmed the diagnosis of exacerbation of corticosteroid-resistant multiple sclerosis and recommended plasma exchanges with albumin as well as a long-term MRI check. Six sessions of plasma exchange were administered. This treatment led to a partial recovery of motor strength, but disorders of superficial and deep sensitivity as well as problems with swallowing persisted. Transit did not resume and feeding was provided by the parenteral route. The respiratory situation still gave rise to concern. The patient passed away in a context of refractory multi-organ failure. The attending physician concluded the subject suffered from exacerbation of corticosteroid-resistant multiple sclerosis, tetraparesis, functional ileus and acute respiratory distress. The relationship of MS relapse to study medication was considered by the investigator possibly related to the study drug.

Case #3

A serious case from Poland concerned a 39-year old male who received 7 doses of treatment (from Oct 2013 to March 2014). Around 3 months after discontinuation, the patient experienced a fulminant MS relapse with neurological deterioration, EDSS score 6.5, with respiratory failure/pneumonia as a consequence. Brain MRI showed numerous areas of elevated signal intensity visible subcortically within remit of white matter, correspondent with demyelinating irregularities at various stages of development. The patient was hospitalized for 4 months for the severe MS relapse and septic shock, EDSS 9.0. Other aetiologies were ruled out. The patient recovered. The events were considered resolved.

Case #4

A serious case from Poland concerns a 34 year old male who, after receiving a year of treatment with daclizumab, experienced an acuter cerebellar syndrome initially attributed to varicella zoster virus and treated with acyclovir with initial improvement; however, varicella zoster virus infection was not confirmed and the patient relapsed with a new episode of severe ataxia and recurrence of acute cerebellar syndrome. PML was discarded. At the time of the last follow up, the event of "acute cerebellar syndrome" was ongoing. No more information is provided.

Case #5

A serious case reported from PL concerns a 24 year old male, who received 20 doses of daclizumab (from Feb 2014 to Oct 2015). One month after the last dose, the patient experienced two attacks of epilepsy. A brain MRI revealed lesions characteristic of a neoplastic process. A histopathological exam of brain tumor puncture was not evident for cancer cells; however, lymphocytic infiltrates especially around the vessels, and dominate T cells and few B cells were found. The investigator ruled out other aetiologies such as PML, tumour and HIV. The final diagnosis was relapse of multiple sclerosis and the study medication was permanently discontinued.

Case #6

A serious case reported in Poland concerns a 48 year-old female treated from Sep 2011 to Nov 2012. Few days later the patient was hospitalised due to epilepsy and *status epilepticus*. In the following days, the frequency of the attacks increased and antiepileptic drugs were initiated with significant

improvement. MS relapse was also reported in this case. There is no additional data provided to assess this case.

The first 5 cases above describe patients treated with daclizumab beta in clinical trials who experienced more serious than expected MS relapses, resistant to conventional treatment with corticosteroids and/or plasmapheresis, 2 of them with fatal outcome. Brain biopsy was performed only in one case, with lymphocytic infiltrates and dominated by T cells, which is consistent with the findings of the post-marketing cases that triggered the referral. In most of the cases other aetiologies were excluded. The characteristics of the events, the result of the tests and the outcome are consistent with the new cases under assessment. The last (6^{th}) case provides scarce information to characterise the event and to assess relationship with daclizumab beta, therefore, it was not taken into account for the conclusion.

ii. Post-marketing

A listing of serious events representing potential lack of efficacy was generated Two cases for further review were identified:

Case #1

A case from Germany concerns a 38 female who received daclizumab treatment for 10 months (Feb to Nov 2017) and few days after the last dose experienced MS exacerbation with paraparesis and status epilepticus; maculopapular exanthema affecting as much as 80% of body surface area, facial oedema, fever, lymphadenopathy and eosinophilia (clinical picture suggestive of DRESS syndrome) and aspiration pneumonia. Due to the patient's condition continuously worsening with *status epilepticus*, the patient was transferred to the ICU, anesthetised, intubated and artificially ventilated. A brain biopsy was performed with plenty of inflammatory infiltrates which were displayed intra-parenchymatous and intramural in the vascular walls. PML and other infections were discarded. According to the physician, analysis of clinical data in comparison with six other patients revealed a largely consistent picture of an excessive immune-mediated CNS reaction caused by daclizumab. The patient died on 06 March 2018.

Case #2

A spontaneous post marketing case reported from Germany concerning a 47 year old female who received daclizumab treatment from March to Oct 2017 (8 months) who experienced a massive exacerbation of MS. The patient experienced severe decompensation of the CNS, requiring hospitalization; the patient was treated with immunosuppressant treatment with high doses of corticosteroids. The patient was diagnosed with meningoencephalitis and remains with severe disability and requires permanent nursing. According to the physician, analysis of the patient's clinical picture in conjunction with six other patients reveals a consistent picture of an excessive immune-mediated CNS reaction caused by daclizumab treatment.

These two cases describe serious relapses of MS resistant to corticosteroid treatment, with devastating complications, and one of them with fatal outcome. Clinical characteristics and tests performed (including brain biopsy in one of them) are consistent with features shared by other patients with similar adverse drug reactions.

C. Other cases potentially related to immune-mediated adverse drug reactions

The MAH was asked to provide a comprehensive cumulative review of cases likely to be related to immune-mediated adverse reactions from studies, spontaneous reports and literature, discussing the biological plausibility based on the known mechanism of action of the product.

As a signal concerning cases of immune-mediated events has been assessed in the context of an ongoing PSUR procedure (EMEA/H/C/PSUSA/00010518/201711). The search of immune-mediated reactions has been extended from 26 May 2017 (cut-off date of the signal in the PSUR) to 01 Mar 2018. An assessment of all immune-mediated events observed with daclizumab therapy up to 01 of March 2018 is provided below.

- *Comparative of the incidence of immune-mediated events observed in the pivotal clinical trials*

Two different searches have been employed to make this comparison. The first one using the High level group term (HLGT) of autoimmune (AI) disorders and the second one expanding this search to other PTs that may represent an immune-mediated aetiology not directly reported in the AE term but evidenced in the clinical details of the event (table below).

Table 1. Comparative of Immune-mediated events in the Pivotal clinical trials

	Search criteria 1: HLGT Autoimmune (AI) disorders (including the PT of Coombs negative haemolytic anaemia and excluding the PTs of multiple sclerosis and optic neuritis)					Broader search: search criteria 1 + PTs* (that could represent immune-mediated disorders)	
	Pivotal Study 205MS201			Pivotal Study 205MS301		Pivotal Study 205MS301	
	Placebo (n= 204)	DAC 150mg (n= 208)	DAC 300mg (n= 209)	IFN beta-1a (n=922)	DAC 150mg (n=919)	IFN beta-1a (n=922)	DAC 150mg (n=919)
Incidence of AI disorders	0%	<1% (n=1)	2% (n=5)	<1% (n=7)	1% (n=11)	6% (n=59)	18% (N=170)
Incidence of serious AI disorders	0%	0%	<1% (n=1)	0%	<1% (n=3)	<1% (n=2)	2% (n=16)

* Included in the analysis of immune-mediated disorders from study 205MS301 were MedDRA PTs associated with the following medical concepts (bolded PTs were included only in this analysis and not included in HLGT of Autoimmune Disorders):

Adrenal insufficiency, Alopecia areata, **Alveolitis**, Ankylosing spondylitis, **Anti thyroid antibody positive, Aphtous stomatitis, Asthma, Atypical pneumonia**, Autoimmune hepatitis, Autoimmune thyroiditis, Basedow's disease, **Blood thyroxine decreased, Blood thyroxine increased, Blood TSH decreased, Blood TSH increased, Celiac disease, Chronic hepatitis, Colitis, Colitis microscopic, Colitis ulcerative, Crohn's disease**, Cutaneous lupus erythematosus, **Cutaneous sarcoidosis, Diabetic ketoacidosis, Diabetes mellitus, Drug reaction with eosinophilia and systemic symptoms, Enteritis, Enterocolitis, Erythrodermic psoriasis, Goitre (or Goiter), Guttate psoriasis, Hemolytic anemia, Histiocytosis haematophagic, Hyperthyroidism, Hypothyroidism, Inflammatory Bowel Disease, Interstitial lung disease, Iridocyclitis, Iritis, Leukocytoclastic vasculitis**, Lupus-like syndrome, **Lymphadenopathy, Lymphadenitis, Lymphoid tissue hyperplasia, Morphea**, Myasthenia gravis, **Myositis, Pancreatitis, Parapsoriasis, Parotid gland enlargement, Parotitis, Periarteritis nodosa, Pericarditis, Pernicious anemia, Platelet count decreased, Pneumonitis, Primary hypothyroidism, Proctitis, Proctocolitis, Proteinuria, Psoriasis, Pulmonary fibrosis, Pulmonary granuloma, Pulmonary sarcoidosis, Pustular psoriasis**, Reiter's syndrome, **Reynaud's phenomenon**, Rheumatoid arthritis, **Sarcoidosis, Scleritis, Seronegative arthritis, Sialoadenitis, Splenomegaly, Spondyloarthropathy, Synovitis**, Systemic lupus erythematosus, **Thrombocytopenia, Thyroiditis**, Type 1 diabetes mellitus, **Uveitis, Vasculitis**, Vitiligo.

The incidence of Autoimmune disorders (total and serious) in the pivotal studies is slightly higher in the daclizumab beta group compared to placebo and IFN groups. When using the broader search, differences increased, observing an 18% of immune-mediated events in the daclizumab group *vs* 6% in the IFN group; however, incidence rates taking into account duration of treatment were not provided by the MAH.

Nevertheless these figures are used as a reference in this assessment. In the pivotal studies, the most common autoimmune events (search 1) in 2 or more subjects were thyroiditis and uveitis. Two subjects in the daclizumab group of the active-compared pivotal study withdrew from the study due to an event and none in the placebo-compared study.

- *Search of immune-mediated disorders in the global safety database: clinical trials (CTs) cases and post-marketing (PM) cases.*

To capture all potential immune-mediated disorders, the MAH performed another search in the global safety database using the following criteria:

- Standardized MedDRA Query (SMQ): Arthritis
- SMQ: Haematopoietic thrombocytopenia
- SMQ: Vasculitis
- SMQ: Thyroid dysfunction
- High Level Group Term (HLGT): Autoimmune disorders plus the following
- Preferred Terms: Abdominal sepsis, Agranulocytosis, Alveolitis, Bacterial sepsis, Bacterial toxaemia, Biliary sepsis, Coeliac disease, Cutaneous lupus erythematosus, Endotoxaemia, Endotoxic shock, Fungal sepsis, Glomerulonephritis, Granulocyte count decreased, Granulocytopenia, Intestinal sepsis, Iridocyclitis, Iritis, Lupus-like syndrome, Morphoea, Multi-organ disorder, Multiple organ dysfunction syndrome, Myasthenia gravis, Myocarditis septic, Myositis, Neutropenic sepsis, Pancytopenia, Parotitis, Pelvic sepsis, Pericarditis, Pernicious anaemia, Pneumonitis, Polyarteritis nodosa, Pseudosepsis, Pulmonary fibrosis, Pulmonary sepsis, Raynaud's phenomenon, Rheumatoid arthritis, Scleritis, Sepsis, Sepsis syndrome, Septic encephalopathy, Septic necrosis, Septic rash, Septic shock, Septic vasculitis, Seronegative arthritis, Sialoadenitis, Systemic inflammatory response syndrome, Systemic lupus erythematosus, Thyroiditis, Toxic shock syndrome, Toxic skin eruption, Type 1 diabetes mellitus, Urosepsis, Uveitis, Viral sepsis, Vitiligo

Non serious cases, cases that concern events associated to MS or optic neuritis and events already identified as expected with daclizumab (AI hepatitis, colitis, cutaneous reactions, lymphopenia, lymphadenoapthy, lymphadenitis and AI haemolytic anemia) were excluded from this analysis.

A total of 66 serious cases were retrieved: 42 from clinical studies, 1 from a non-interventional study, 12 from solicited sources, and 11 from spontaneous sources.

Among the 42 cases from clinical trials, the most common reported events affect muscular and connective tissue (arthritis, Still's disease, Reiter's syndrome and psoriatic arthropathy), blood system (cytopenias), nervous system (myasthenia gravis), endocrine system (hyperthyroidism), and gastrointestinal system (celiac disease) in this order.

Among the 24 cases from post-marketing sources, the most common reported reactions affect muscular and connective tissue (systemic lupus erythematosus, polymyalgia rheumatic, arthritis, Behcet's syndrome, ankylosing spondylitis), nervous system (encephalitis autoimmune, acute disseminated encephalomyelitis, myelitis transverse), blood system (cytopenias), endocrine system (thyroid disorders), skin and subcutaneous tissue (pyoderma gangrenosum, pemphigoid), eye (autoimmune uveitis), respiratory tract (alveolitis), renal system (glomerulonephritis) and infections (sepsis) in this order.

Subjects' mean age is very similar in cases from both clinical trials and post-marketing experience at around 43 years old, and in both settings there is a preponderance of female patients as expected considering the epidemiology of the disease. On the contrary, mean time to event onset differs being 748 days in CT cases and 141 days in PM cases. In two fatal cases the cause of death was the immune-mediated process, one observed in CTs in a patient who died of pancytopenia and multiple organ dysfunction syndrome and the other in the PM setting concerning a patient with fatal autoimmune encephalitis and status epilepticus.

<u>Serious autoimmune disorders</u>

The first search strategy included the HLGT Autoimmune disorders. A wide range of different autoimmune processes was retrieved covering the PTs of encephalitis autoimmune, systemic lupus

erythematous, autoinmune disorder, acute disseminated encephalomyelitis, alveolitis, ankylosing spondylitis, autoimmune uveitis, glomerulonephritis, myelitis transverse, pemphigoid, polymyalgia rheumatica, and pyoderma gangrenosum.

The five cases retrieved with this search that reported neurological involvement have been described above. Cases involving thyroid (2 cases) or arthritis (5 cases) have been moved to the assessment of endocrine disorders and muscular and connective tissue disorders assessment respectively to get a complete picture of all similar cases together. The main autoimmune disorders identified are as follows:

- Glomerulonephritis: three cases, two from clinical trials and one solicited case have been retrieved. All presented temporal plausibility and two of them resolved after daclizumab discontinuation and supportive treatment (outcome was unknown in one case). Two cases had confounding factors (a previous episode of nephrotic syndrome and glomerulonephritis mesangialis proliferative in one case and treatment with lithium in the other). The third case was biopsy confirmed, presented reasonable temporal relationship and no confounding factors or alternative cause. Moreover, more patients in the daclizumab group in the CT 205MS301 reported proteinuria (6 patients DAC group vs 2 patients in IFN group) what could be a symptom of glomerulonephritis; Nephrotic syndrome and glomerulosclerosis are labelled ADRs for IFN. At this stage the evidence to support a causal relation between daclizumab and glomerulonephritis is limited, but the higher frequencies of proteinuria cases in CTs compared to IFN and the role of daclizumab in immune-mediated disorders due to its mechanism of action, may indicate a possible underlying immunological mechanism daclizumab-mediated.
- Celiac disease: two cases with the PT of celiac disease have been retrieved. Both cases appeared temporally associated with treatment and clinical symptoms were suggestive of celiac disease but colonoscopy was performed only to one subject and in this case the event resolved despite no action was taken with the drug. No cases of celiac disease were observed in the active compared pivotal study either in the DAC group or IFN group. At this stage the evidence to support causal association is scarce not allowing drawing conclusions.
- Lupus-like syndrome: one isolated serious case of potential drug-induced lupus erythematosus was observed in the CT setting. The subject presented predominant skin involvement, the outcome was temporally related to drug exposure and resolved after drug discontinuation; however, laboratory work-up do not support the drug-induced origin due to negative test for ANA and anti-DS DNA antibodies at the time of the report. Other two cases of systemic lupus erythematosus were retrieved with this search but both lack relevant information. Within clinical trials, one case of systemic lupus erythematosus and another of cutaneous lupus erythematosus were reported in the daclizumab group of 205MS301 CT with no corresponding cases in the IFN group. Despite the limited number of cases, the imbalance observed in clinical trials suggests a possible role of daclizumab. Systemic lupus erythematosus is a labelled ADR for IFN.
- Type 1 Diabetes mellitus: case concerning a 49-year-old female patient in a CT diagnosed of type 1 DM after 19 doses of daclizumab. At the time of event onset the patient also experienced exanthema, fever, elevated LFTs and ANA test was positive. These events presented temporal relationship with daclizumab treatment; the subject had no medical history predisposing to this condition that developed concurrently with other events suggesting an underlying immune-mediated mechanism. Diabetic disorders in the daclizumab group were similar to IFN group in the pivotal active-compared study 205MS301. Despite there is a single case and no imbalance of this event was observed in CTs, in the light of the above information causal association cannot be ruled out.

- Other reports: myasthenia gravis (1 subject) iritis (1 subject), penphigoid (2 subjects), autoimmune disorder (2 subjects), alveolitis (1 subject), pyoderma gangrenosum (1 subject), myelitis transverse (1 subject), Guillain Barre syndrome (1 subject), pulmonary fibrosis (1 subject), autoimmune uveitis (1 subject), systemic sclerodermia (1 subject) presenting limited information precluding the assessment.

Muscular and connective tissue disorders

Under this section all cases reporting arthritis have been assessed. This information is disaggregated in different sections in the responses to question 3: 5 cases in the search of serious autoimmune disorders, 9 cases in the search of SMQ Arthritis from clinical trials and 2 cases using the same search from spontaneous sources. All these cases are compiled and summarized in the table below:

Table 2 Summary of cases retrieved by search of SQM Arthritis

TERM	AGE/ SEX TTO SETTING	MEDICAL HISTORY/ LABELLED CONC MED *	ADR SYMPTOMS	LAB. RESULTS	ACTION TAKEN DRUG	OUTCOME
Arthritis	24Y/F 22 doses CT	Traumatic arthritis Doxycycline * Lornoxicam * Celecoxib * Omeprazol *	Joint swelling and pain. Progression of arthralgia, swelling of lower extremities, deteriorating mobility	Thrombocytosis HLA B27 – Chlamydia Ab +	Withdrawn	Ongoing
Arthritis	47Y/F 20 doses CT	Arthritis of right knee and pain in left knee since Dec 2016	Recurring effusion into the right knee and pain in both knees and joints in the right foot, minor oedema of right 2nd and 4th toes	ANA/ANCA positive	No change	Ongoing
Reiter's syndrome	31Y/M 20 doses CT	Sulfamethoxazol/ trimethoprim * Moxifloxacin **	Urethritis, conjunctivitis, filiform keratitis in both eyes. Sialadenitis Arthritis in right talocural joint	HLA B27 - UTI Chlamydia Ab + Negative infectious etiology workup Lymphadenopathy Leukocytosis Neutrophilia Agranulocytosis	Temporarily discontinuation	Ongoing
Reiter's syndrome	42Y/ M 79 doses CT	None	Conjunctivitis Polyartheritis	Possible UTI ANA mildly + Negative infectious etiology workup Elevated CRP	Withdrawn	Ongoing
Reactive arthritis	34Y/ F 65 doses CT	Gastroenteritis Allergic dermatitis Gilbert's syndrome Fludrocortisone * Fluoxetine * Clindamycin***	Arthritis Acute gastroenteritis	Thrombocytosis Elevated CRP ANA + IgG Campylobacter + EBV-CA IgG + EBNA IgG + EBV EA IgG borderline	Withdrawn	Ongoing Symptoms reduced by stopping Zynbryta and starting steroid
Polyarthritis	49Y/ M 16 doses CT	Obese Hypotension	Psoriasis Polyarthritis Dactylitis Swollen wrist and ankles Knee crepitation	None reported	No change	Ongoing
Polymyalgia rheumatica	60Y/F Non-interventional study	Arthralgia, back pain, bursitis, chondrocalcinosis pyrophosphate, meniscus injury, osteoarthritits, spondylo-arthropathy Pantoprazole *	Multiple joint arthralgia and decreasing range of moion	Erythrocyte sedimentation rate and C-reactive protein increased	Withdrawn	Not recovered Confounded by medical history
Arthritis	38Y/F Spontaneous	Levothyroxine*	Arthritis of knee joint both sides	Erythrocyte sedimentation rate and C-reactive protein increased	Permanently discontinued	Recovering Positive dechallenge

Ankylosing spondylitis	48Y/F Non-interventional study	None reported	Back pain reported radiated in arms, pain and cramps in left thigh.	Tested positive for HLA B27	Unknown	Not recovered Case lacking relevant information
Arthralgia	45Y/M 23 doses CT	Peripheral paresis of nerve VII Hyper-lipoproteinemia, Dystopia of left kidney Itchy exanthema	Fever, generalized toxoallergic exantema	Elevated bilirrubin Elevated WBC	No change	Resolved (probably infection-related) Unlikely
Still's disease	34Y/ M 26 doses CT	Allergic to pollen and penicillin	Arthritis Sore back, sore joints	Thrombocytopenia Lymphopenia	Temporarily discontinuation	Resolved Positive dechallenge
Still's disease	43Y/ F 125 doses CT	None reported	Polyarteritis Myalgia Arthralgia	None reported	Temporarily discontinuation and then restarted	Ongoing Positive rechallenge
Psoriatic arthritis	45Y7 F 37 doses CT	Keratitis Psoriasis	Pain/ swelling metacarpophalangeal joints Recurrent keratoconjuntivitis	Leukocytes low ANA +	Temporarily discontinuation and then restarted	Ongoing
Olygoarthritis seronegative	28 Y/ F 32 doses CT	Conjuntivitis Folliculitis Hasimoto thyroiditis Pain and swelling of joints Knee pain Goiter	Stiffness and pain in shoulder, swelling and pain in knees, hands and feet, pain in jaw, metatarsophalangeal joints sensitive to touch	ANA + HLA B27 – HLA B51 -	Temporarily discontinuation	Ongoing
Rheumatoid arthritis Final diagnosis of phiysician was seronegative arthritis	56Y/M 25 doses CT	Asthenia Depression	Cutaneous lesions and balanitis Polyarthritis of the knees and elbows NSAIDs had Little effect	Joint fluid aspiration showed inflammation without crystals or bacteria Viral infection was ruled out Anti-cyclic citrullinated peptide (CCP) and ANA rheumatoid factors were negative	Withdrawn	Not recovered but improved after discontinuation
Rheumatic disorders	Adult/M Spontaneous	None reported	Psoriasis and skin rash	NR	Permanently discontinued	Recovered

Medication labelled for arthralgia, arthritis** or polyarthritis ****

A total of 16 cases, 14 of them from studies (12 from CTs and 2 from a non-interventional study) and 2 from spontaneous sources have been retrieved from the global safety database. Of these cases, one is reported unlikely as aetiology is apparent, nine cases presented confounding factors or lack of relevant information precluding the assessment and the last six cases did not have clear alternative causal agent/confounding factors.

Among the cases presenting confounding factors, five patients were concomitantly taking medication labelled for arthralgia, arthritis or polyarthritis and in three cases an urinary tract infection (UTI) was detected (two with positive test for Chlamydia antibodies). In should be noted that UTI is a common complication in MS patients and it could occur parallel to the arthritic disorder but not necessarily causing it. In two cases no action was taken with daclizumab and the event was ongoing but in other two cases in which a different aetiology is apparent, improvement/recovery of arthritis episode with daclizumab discontinuation was reported. Four subjects did not recover despite drug discontinuation and in the last case action taken with the drug is unknown.

Selecting the 6 cases (last in the list in table above) without clear confounding factors, 5 from clinical trials and 1 from spontaneous source, it is observed that all of them presented temporal association and no clear alternative causative agent, one patient reported positive rechallenge, other two subjects reported positive dechallenge and in another one the event improved after daclizumab discontinuation. The remaining two patients did not recover after drug discontinuation. Two of these cases reported ANA positive, another had CCP and ANA rheumatoid factors negative and this data is unknown for the other three.

When comparing adverse events belonging to the SOC musculoskeletal and connective tissue disorders in the pivotal active compared study, an imbalance between IFN and daclizumab groups is observed.

Table 3. Potential Immune-mediated disorders in 205MS301 Study

	IFN beta-1a 30 mcg N=922	DAC 150 mg N=919
Musculoeskeletal and connective tissue disorders	1 (<1%)	9 (<1%)
Myositis	0	2 (<1%)
Spondyloarthropathy	0	2 (<1%)
Lupus-like syndrome	0	1 (<1%)
Rheumatoid arthritis	0	1 (<1%)
Seronegative arthritis	0	1 (<1%)
Synovitis	0	1 (<1%)
Systemic lupus erythematosus	0	1 (<1%)
Ankylosing spondylitis	1 (<1%)	0

Subjects are counted only once
Include events started between first dose and up to 180 days after last dose

Cases of spondyloarthropathy, rheumatoid arthritis and seronegative arthritis were observed in the daclizumab group with no corresponding case in the IFN group. Only one case of ankylosing spondylitis was reported in the IFN group. The ADRs of arthralgia and arthritis are labelled for IFN.

Overall, in this review six medically confirmed cases with no relevant medical history or concomitant medication, no confounding factors or alternative causative agent, and with temporal plausibility with the event were detected. In one subject the biopsy result (fluid joint aspiration) confirmed an immunological process that correlated with the known safety profile of daclizumab and one positive rechallenge and two positive dechallenges gives strength to the association. Additionally, other 8 cases with certain level of confounding factors (concomitant medication, infections) in which daclizumab involvement cannot be completely ruled out and a misbalance observed in the active-compared study with IFN (labelled for arthritis) support the causality of the process.

Characteristics of seronegative arthritis are genetic predisposition (HLA27 positive) and respond normally to NSAIDs. Three patients presented negative HLA B27 status and another case reported not improvement after NSAIDs therapy. These facts, together with the lack of infectious aetiology found in 10 cases make immune-mediated arthritis more likely. It is noticeable that in 5 cases concurrent elevation of liver function tests or lymphadenopathy or haematological discrasias were identified that are processes with an underlying immune-mediated mechanism already associated to daclizumab therapy. In the light of this evidence, the role of daclizumab on the occurrence of these reactions is possible

Endocrine disorders

The MAH has performed a search of thyroid disorders using the SMQ Thyroid disorders. This information is disaggregated in different sections in the responses to question 3 and there are inconsistencies between the number of cases referred in the text and those tabulated in the appendix.

Also, in the recently assessed PSUR there was an extra case of thyroid disorders not included in this review. All the information coming from the different section in this response and the PSUR is compiled and evaluated. There are 6 cases of thyroid disorders in patients on daclizumab treatment (4 cases from clinical trials and 2 from spontaneous sources).

However, 5 out of 6 cases were not considered related, and the 6th case referred to a worsening of a previous of a Basedow's disease, although with involvement of liver and leukopenia.

Number of thyroid disorders (serious and non-serious) observed in the active compared study 205MS301 is similar in IFN and daclizumab treated patients. IFN is labelled for hypothyroidism and hyperthyroidism with unknown frequency.

Blood disorders

A search in the global safety database using the SMQ Haematopoietic thrombocytopenia was employed and 4 serious cases from CTs have been retrieved. No cases from spontaneous sources have been obtained with the same search.

In the last PSUR (period 27 May 2017 to 26 November 2017) a cumulative review of cytopenia cases was submitted providing more complete information and includes three of the cases submitted also within the MAHs responses to the Article 20 referral procedure.

No relevant effects of daclizumab beta on haematology or coagulation parameters were observed in the preclinical phase studies.

In clinical trials, an imbalance of cytopenia cases between daclizumab and placebo and active control group was detected when pooling all data collected through 26 Nov 2017 (table below):

Table 4. Comparison of cytopenia events in daclizumab, placebo and Interferon Beta-1a treated Patients from daclizumab clinical trials

MedDRA PT	Placebo[1] n (%) (N=204)	interferon beta-1a[2] n (%) (N=922)	Daclizumab[3] n (%) (N=2251)
Number of subjects with a cytopenia adverse event	2 (<1)	91 (10)	279 (12)
Anaemia	1 (<1)	28 (3)	110 (5)
Lymphopenia	0	31 (3)	56 (2)
Lymphocyte count decreased	0	10 (1)	51 (2)
Leukopenia	0	13 (1)	31 (1)
Haemoglobin decreased	1 (<1)	9 (<1)	20 (<1)
White blood cell count decreased	0	12 (1)	14 (<1)
Neutropenia	0	9 (<1)	14 (<1)

Thrombocytopenia	0	1 (<1)	16 (<1)
Neutrophil count decreased	0	11 (1)	11 (<1)
Platelet count decreased	0	2 (<1)	8 (<1)
Microcytic anaemia	0	2 (<1)	7 (<1)
Red blood cell count decreased	0	4 (<1)	6 (<1)
Agranulocytosis	0	0	4 (<1)
Monocyte count decreased	0	7 (<1)	4 (<1)
Pancytopenia	0	0	4 (<1)
Haematocrit decreased	0	3 (<1)	3 (<1)
Febrile neutropenia	0	0	1 (<1)
Granulocytopenia	0	0	1 (<1)
Lymphocyte count abnormal	0	0	1 (<1)
T-Lymphocyte count decreased	0	0	1 (<1)

Notes:
1 – Data from study 205MS201, where a total of 204 subjects received placebo
2 – Data from study 205MS301, where a total of 922 subjects received interferon beta-1a
3 – Data from pooled studies 205MS201, 205MS202, 205MS203, 205MS301, 205MS302, 205MS303 and 205MS305, including 1958 subjects who received DAC 150 mg and 293 subjects who received DAC 300 for a total of 2251 subjects.
PT = Preferred Term

The most frequently reported cytopenias in the daclizumab beta group were anaemia and lymphopenia, both already covered by the approved EU SmPC. The other most common serious events were thrombocytopenia, pancytopenia, agranulocytosis and leukopenia that are not included in the SmPC.

The assessment of cases provided below is focused in those retrieved in the clinical trial setting, as the search from the post-marketing experience did not bring useful information

Six serious thrombocytopenia cases from clinical trials were reported, two of them provided alternative causality (secondary to human immunodeficiency virus) or considered not related as the event abated while on daclizumab therapy thus discarded from the analysis. Regarding the 4 remaining cases, three of them concern female patients between 35 and 41 years old and the fourth belong to a 53-year-old male patient; all developed thrombocytopenia while on daclizumab and in all cases the investigator considered the events as related to treatment. Three have some level of confounding with the presence of concomitant medication labelled for the ADR (carbamazpine and citalopram) or relevant medical history (tendency toward thrombocytopenia and development of active hemorrhagic syndrome) and in the fourth no clear alternative agent or confounding factor was detected. Time to onset ranged between 11 and 54 doses, in two of them an extensive laboratory workup excluded the infectious aetiology of the ADR and two patients improved after rituximab and/or steroid treatment and after daclizumab discontinuation. One investigator specifically mentioned in the case the autoimmune origin of the thrombocytopenia and in two cases the ADR developed concurrently with other ADRs such as increased liver function tests, haemolytic anaemia or lymphadenopathy.

Overall, six cases of serious thrombocytopenia events were detected during clinical trials in the daclizumab group and none in the placebo or active comparator groups. This misbalance observed in the clinical studies together with the reported temporal relation, the lack of clear alternative causes and the biological plausibility with the autoimmune origin of this and other ADRs occurring concurrently and already described for daclizumab therapy provide support for a causal association.

Four serious cases of pancytopenia were detected in clinical trials one of them evolved to multiorgan failure and death. These cases involved patients between 33 and 44 years old, two females (unknown gender in the other two). Time to onset ranged from 23 to 160 doses. Three of the cases have a

certain degree of confusion, one subject had presented a previous episode of neutropenia but apparently recovered while on treatment with daclizumab, concomitant doxycycline therapy was reported in another case and the last one had a urine culture positive for *e.coli* which could have triggered the events. Extensive laboratory workup was reported in three cases and did not identify any infectious agent and two cases had also results of bone marrow biopsy that ruled out a malignant blood disease. The four cases were considered related to the study drug by the investigators and the four subjects experienced concurrent immune-mediated disorders such as haemolytic anaemia and autoimmune hepatitis or other symptoms suggesting immune disorder (elevated LFTs and lymphadenopathy) at the same time than the event onset. The three non-fatal cases improved after corticosteroid therapy.

Overall, the four cases presented temporal plausibility and no clear alternative causal agent was identified. The fact that the ADR developed concomitantly with other immune-mediated disorders known for daclizumab, support the biological plausibility of the event and the autoimmune origin of the haematological finding as well.

Vascular disorders

The search performed with the SMQ vasculitis retrieved 3 serious cases from clinical trials and one from spontaneous sources. In the last PSUR there was an extra serious case of polyartheritis nodosa that is included in this assessment thus there are a total of 4 cases from CTs and 1 from PM sources. The 4 cases from CTs are described with the following PTs: vasculitis (1), hypersensitivity vasculitis (1), kawasaki disease (1) and polyarteritis nodosa (1). In three cases, the events resolved after daclizumab discontinuation and steroid treatment (positive dechallenge), and one had a negative rechallenge. Time to onset ranged between 9 and 35 doses (mean 24 doses). Necrotizing leukocytoclastic vasculitis was confirmed by biopsy in 2 cases. Three cases were assessed as related to daclizumab treatment by the HCP. The MAH has performed causality assessment with the WHO methodology categorizing 1 of these cases as possibly related to daclizumab, 1 as probably related and the remaining 2 cases as unlikely related to daclizumab.

The case from post marketing sources reported the PT term of Behcet's syndrome however the lack of relevant information make the case not assessable.

Table 5. Potential Immune-mediated disorders in 205MS301 Study

	IFN beta-1a 30 mcg N=922	DAC 150 mg N=919
VASCULAR DISORDERS	1 (<1%)	3 (<1%)
Vasculitis	0	3 (<1%)
Raynaud's phenomenon	1 (<1%)	0

Subjects are counted only once

Include events started between first dose and up to 180 days after last dose

Overall, cases from clinical trials presented temporal association to daclizumab treatment, diagnose was confirmed by biopsy in two cases, positive dechallenge and were judged as related to daclizumab beta in three instances and with WHO methodology in two cases. Cases resolved upon steroid treatment suggesting an immune-mediated mechanism. The frequency observed in the active-compared pivotal study yielded higher figures of vascular disorders in the daclizumab group vs IFN-treated patients with 3 cases of vasculitis in the daclizumab-treated subjects with no corresponding case in the IFN group. IFN is not labelled for vasculitis.

Multiple organ dysfunction syndrome

In this section the MAH has provided information on 5 serious cases from CTs and 3 additional cases from post marketing sources. Seven of these cases reported reactions/events involving cytopenias and have been included and commented above in the blood disorders section. The cases present complex clinical pictures with multiple symptoms affecting multiple organ/systems such as skin, kidney, spleen, blood etc; in one case an extreme immune response was observed. No clear causal agent was detected in any case apart from daclizumab therapy. Three of these cases evolved to multiple organ dysfunctions but this can be considered a consequence of the immune disorder that massively affects other or organ/systems and one had a fatal outcome.

The eighth case concerns a 46 year-old male patient from a non-interventional study in the USA reported a sepsis concomitantly to other organ involvement such as elevated liver function tests, lymphadenopathy and rash. This consumer-reported case lacks relevant information precluding the full assessment.

Conclusions

For the blood disorders, due to temporal relationship of the events of thrombocytopenia and pancytopenia to daclizumab beta, a potential underlying immune-mediated process compatible with the known mechanism of action of daclizumab and the lack of a clear confounding factor or alternative causal agent, the role of daclizumab is plausible. The higher frequency of blood dyscrasias in the pivotal clinical trials supports the association.

Vascular disorders from clinical trial cases presented temporal association to daclizumab treatment, diagnose which was confirmed by biopsy in two cases, positive dechallenge and were judged as related to daclizumab beta in three instances and with WHO methodology in two cases.

The cases reporting multiple organ dysfuction presented complex clinical pictures with multiple symptoms affecting multiple organ/systems such as skin, kidney, spleen, blood etc; the causal agent detected was daclizumab therapy.

Conclusions on Safety

According to the information provided, 18 cases of immune-mediated adverse events (7 from clinical trials and 11 spontaneous cases) involving the central nervous system have been identified. These cases share the same clinical picture including: more severe than expected relapse of multiple sclerosis, resistant to treatment with corticosteroids and/or plasmapheresis, unexpected findings in the brain biopsies when performed and devastating or fatal outcome in most of the cases (6 fatal, 4 severe disabilities). Of note, some of these patients also experienced some symptoms of DRESS syndrome.

All patients share a common clinical picture of serious MS relapse, resistant to corticosteroid and plasmapheresis treatments, torpid evolution, serious, or fatal outcome and, when biopsies were performed they presented unexpected findings.

From drug development studies and along post authorisation phase an increasing number of immune mediated disorders have been associated to daclizumab beta. In this review of other immune-mediated events, other adverse reactions with an underlying immunological mechanism appeared in daclizumab-treated patients; there is an extensive array of processes that can involve different organs/systems of the body. In this review, immune-mediated processes implying muscular and connective tissue, blood, vascular system, and renal system, have been identified. Some of the cases show a complex clinical picture involving different organs at the same time and in some cases can evolve to fatal outcome.

While the exact physiopathological mechanism by which daclizumab beta cause this immune-mediated events involving CNS, and muscular and connective tissue, blood, vascular system and renal system remains unknown, it is proved that daclizumab trigger immune-mediated events such as hepatitis or autoimmune haemolytic anaemia, among others. It is highly unlikely that the patients analysed in this referral would have experienced these symptoms without a common thread and that these findings were explained by random. Taken together the known potential of daclizumab to trigger immune-mediated events and the unexpected findings of patients sharing a common clinical picture, it is clear that daclizumab plays a key role in the development of the serious immune-mediated CNS ADRs.

Based on the data analysed in this review, there is high evidence supporting the involvement of daclizumab beta as a trigger of immune-mediated adverse reactions with devastating consequences. The most critical immune-mediated events involve the central nervous system, but are also patent in the liver, skin, connective tissue and blood, among others.

3. Benefit-risk balance

Daclizumab was first approved for the treatment of relapsing forms of multiple sclerosis in the EU in July 2016 through a centralised procedure.

During the previous safety referral (Ref. EMEA/H/A-20/1456/C/003862/0018), the PRAC concluded that daclizumab was associated with a potentially fatal risk of immune-mediated liver injury. No time window of a higher risk could be identified and cases of liver injury had occurred throughout treatment and up to 6 months after the last dose of daclizumab. Risk or predictive factors that may play a role on the occurrence of liver damage such as comorbidities, relation with dose, timing, genetic or biochemical markers could not be identified. Overall, considering the data available, the occurrence of daclizumab induced liver injury was considered to be unpredictable. As a consequence of a previous referral on daclizumab and the risk of immune-mediated serious liver damage, indication was restricted 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 any other DMT is contraindicated or otherwise unsuitable. Furthermore, other RMM were implemented such as contraindication in patients with pre-existing hepatic disease or impairment, strengthening the warnings to take due account that liver functions.

The mechanism of action of daclizumab beta is complex. Daclizumab binds to the alpha-subunit (CD25) of the high-affinity interleukin-2 (IL-2) receptor. IL-2 is a T-cell growth factor with mitogenic effect on T cells and is produced by activated T-cells. Activation of T-cell receptors increases high affinity IL-2 receptor stimulating the proliferation and differentiation of T cells and the secretion of pro-inflamatory cytokines. Daclizumab 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 latter 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. These CD56 NK cells are able to gain access to the central nervous system in MS and kill autologous activated T cells. It has been hypothesised that autoimmunity secondary to daclizumab treatment could be associated with the reduction of CD4+CD25+Foxp3+T-regs; it is theoretically possible that a decrease in the number of regulatory T cells and activation and expansion of NK cells may result in an increased risk to develop immune-mediated events. Moreover, it is known that subjects with congenital CD25 deficiency frequently develop immune-mediated disorders and expansion of auto-reactive T cell clones have been found in thymic tissue from these CD25-deficient patients. It was also noted that other

immune-mediated conditions and autoimmune conditions had been reported in clinical trials, in some cases being numerically higher than the comparison group.

Therefore, even when there is high evidence supporting the involvement of daclizumab beta as a trigger of immune-mediated adverse reactions, and the mechanism of action of daclizumab supports this fact, the exact physiopathological mechanism by which daclizumab beta triggers these immune-mediated events remains uncertain.

The current safety referral (EMEA/H/A-20/1462/C/003862/0018) was triggered based on cases of inflammatory brain disorders. During this review, the MAH was requested to present and analyse detailed information on all cases of central nervous system adverse drug reactions, including cases of lack of efficacy, in clinical trials and spontaneous reporting. After the assessment of the information, 18 cases were retrieved for further analysis. These cases share the same clinical picture including: more severe than expected relapse of multiple sclerosis, resistant to treatment with corticosteroids and/or plasmapheresis, unexpected findings in the brain biopsies when performed and devastating or fatal outcome in 10 of these 18 cases. Of note, some of these cases also experienced symptoms of DRESS syndrome. Although the specific physiopathological mechanism by which daclizumab causes immune-mediated disorder involving CNS remains unknown, it is highly unlikely that the patients analysed in this referral would have experienced these symptoms without a common thread and these findings were explained by random. Taken together the known potential of daclizumab to trigger immune-mediated events and the unexpected findings of patients sharing a common clinical picture, it is clear that daclizumab plays a key role in the development of the serious immune-mediated CNS ADRs

In addition, the MAH was also requested to present cases of immune-mediated adverse reactions. Other adverse reactions with an underlying immunological mechanism appeared in daclizumab-treated patients; there is an extensive array of processes that can involve different organs/systems of the body. In this review, immune-mediated processes implying muscular and connective tissue, blood, vascular system, and renal system, have been identified. Some of the cases show a complex clinical picture involving different organs at the same time and in some cases can evolve to fatal outcome.

As already seen previously, serious cases of immune-mediated liver injury can occur with hepatocellular pattern highly suggestive of an autoimmune mechanism, broad time to onset, even after treatment discontinuation, which are no predictable and no preventable in clinical trials and spontaneous reporting.

In summary, due to the seriousness of the cases with fatal or devastating outcome, the fact that they are unpredictable and not preventable, the evidence supporting the role of daclizumab beta in triggering this immune-mediated events, the PRAC confirmed its initial recommendation and considers that the benefit-risk balance of daclizumab beta is not favourable.

4. Risk management

4.1. Pharmacovigilance activity

4.1.1. PSUR monitoring

The last PSUR (period 27 May 2017 to 26 November 2017) is currently under assessment. Although the product has been revoked from the market (27 March 2018), it is important that the scientific assessment of this PSUR is finalised.

In view of the time that it is needed for any of the adverse events discussed in this review to manifest the PRAC asks the MAH to submit for assessment a last PSUR for Zinbryta for further assessment. A Data lock point (DLP) of 31 October 2018 will be acceptable, in order to capture any late events.

5. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for Zinbryta,
- The PRAC recommended provisional measures on 6 March 2018 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 to suspend the use of the product and the marketing authorisation, as well as recalling the batches of the product at the level of pharmacies and hospitals.
- The PRAC reviewed the totality of the available data, including data provided by the marketing authorisation holder in writing on safety data from clinical trials and post-marketing in relation to the overall risk of immune-mediated disorders, including adverse drug reactions with CNS involvement in treatment with Zinbryta.
- In addition, PRAC also considered the known serious immune-mediated liver toxicity associated with Zinbryta as well as other immune-mediated disorders affecting other organs than the brain or the liver.

The PRAC concluded that daclizumab beta is associated, during the treatment and for several months (i.e. at least 6 months) after the end of treatment, with an unpredictable and potentially fatal risk of immune-mediated disorders including CNS, liver and other organs. In view of the above, the PRAC confirmed its initial recommendation that the benefit-risk balance of Zinbryta is no longer favourable.

The PRAC noted the Commission Decision of withdrawal of the marketing authorisation at the MAH's request adopted on 27 March 2018.