

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Review Completion Date	May 27, 2016
Subject	Evaluation of REMS proposal
Established Name	Daclizumab
(Proposed) Trade Name	Zinbryta™
Applicant	Biogen Idec
Formulation(s)	150 mg/mL Injection pre-filled syringe
Dosing Regimen	150 mg subcutaneously once monthly
Proposed Indication(s)	Treatment of patients with relapsing forms of multiple sclerosis.

*** This document contains proprietary information that cannot be released to the public***

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for daclizumab, a 351(a) Biologic,¹ is necessary to ensure the benefits of the product outweigh the risks. AbbVie Inc. (AbbVie) submitted a Biologic Licensing Application (BLA 761029) for daclizumab on February 27, 2015, for the treatment of patients with relapsing forms of multiple sclerosis (MS). Ownership of the BLA was subsequently transferred to Biogen Idec (Biogen). The major risks associated with the use of daclizumab are drug-induced liver injury including autoimmune hepatitis, and serious immune mediated disorders, such as non-infectious colitis, various skin reactions, and other events.

The risks of severe hepatic injury and immune mediated disorders associated with daclizumab are serious, and a REMS is required to ensure that the benefits of the product outweigh the risks. The goal of the program is to mitigate the risks of severe and fatal hepatic injury and serious immune-mediated disorders. The key reasons for the REMS are to ensure prescribers and patients are educated and informed about the serious risks and safe use conditions, the need for monthly monitoring and evaluation by the prescriber, and the need to enroll all patients in a registry to obtain to better inform about the risks. After considering recommendations from the REMS Oversight Committee, DRISK and the Division of Neurology Products (DNP) determined the REMS would require a communication plan and elements to assure safe use (ETASU) including that health care providers who prescribe the drug are specially certified; pharmacies that dispense the drug are specially certified; the drug be dispensed to patients with evidence or other documentation of safe-use conditions; each patient using the drug be subject to certain monitoring; and that each patient using the drug is enrolled in a registry.

The Applicant was informed of our determination regarding the need for an ETASU REMS on March 16, 2016. Drafts of the REMS document, materials, and supporting document were subsequently negotiated between the Agency and Biogen by email communications and teleconferences. Biogen submitted a REMS amendment to the BLA on May 27, 2016, via email and global submit. The amended proposed REMS consists of a communication plan; ETASU that include prescriber certification, pharmacy certification, documentation of safe-use conditions, patient monitoring, and a registry with mandatory enrollment of patients; an implementation system; and a timetable for submission of assessments. On May 27, 2016, Biogen submitted an amended REMS and appended materials that are acceptable; therefore DRISK recommends approval of the REMS submitted on May 27, 2016.

¹ FDAAA factor (F): Whether the drug is a new molecular entity.² FDAAA factor (D): The expected or actual duration of treatment with the drug.

1 Introduction

AbbVie submitted a Biologic Licensing Application (BLA 761029) for daclizumab on February 27, 2015, for the treatment of patients with relapsing forms of multiple sclerosis. The Applicant initially proposed a REMS that consists of a Medication Guide, communication plan (CP), and a timetable for submission of assessments. Biogen, who subsequently assumed ownership of the BLA, submitted a proposed REMS amendment with ETASU on May 27, 2016. Biogen's amended REMS proposal was based on advice from the Agency (via teleconference) subsequent to a REMS Oversight Committee (ROC) meeting held in March 2016 that the determination was made that a REMS with ETASU would be necessary to ensure the benefits of their drug outweigh its risks. The applicant's amended proposal submitted by email on May 27, 2016, is acceptable to DRISK and therefore we recommend approval of the REMS and appended materials.

2 Background

2.1 PRODUCT INFORMATION

Daclizumab, a new molecular entity, is a humanized IgG1 monoclonal antibody (mAb) that binds to CD25, a lymphocyte surface receptor for Interleukin-2 (IL-2) that is characterized as a T-cell growth factor. The precise mechanism of action of daclizumab in the treatment of relapsing multiple sclerosis, the proposed indication, is unknown. Modulation of IL-2 signaling by daclizumab may result in expansion and activation of immunoregulatory natural-killer cells that gain access to the central nervous system and kill activated T cells involved in the inflammatory process. Of note, additional regulatory T-cells that suppress autoimmunity may also be impacted by the product. Daclizumab is available as a 150 mg/mL, single-dose, pre-filled syringe intended for chronic treatment as a once monthly subcutaneous (SC) injection,² and is likely to be administered by patients or caregivers in the home setting. The pharmacodynamic effects of daclizumab range from 4–6 months in duration. Although daclizumab is not currently licensed in any country, the European Medicines Agency, Committee for Medicinal Products for Human Use, recommended granting a marketing authorization for the treatment of relapsing multiple sclerosis on April 28, 2016.

A separate daclizumab product that was produced (b) (4) and marketed as Zenapax, was approved in the U.S. in 1997 for the prophylaxis of acute organ rejection in patients receiving renal transplants. Zenapax was administered intravenously as part of an immunosuppressive regimen that included cyclosporine and corticosteroids. Marketing of the drug was discontinued in 2009 for commercial reasons and the BLA was withdrawn in February 2015.

² FDAAA factor (D): The expected or actual duration of treatment with the drug.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761029 relevant to this review:

- 11/07/2014: Pre-BLA meeting minutes state the Applicant was informed that the need for a REMS will be determined during review of the application.
- 02/27/2015: BLA 761029 submission for the treatment of patients with relapsing forms of multiple sclerosis was received. The submission includes a REMS that consists of a Medication Guide, communication plan, and timetable for submission of assessments, to mitigate the risk of severe hepatic injury.
- 04/02/2015: Major amendment to provide patient profiles for all subjects who met the criteria for a safety narrative was received by the Agency.
- 05/12/2015: Ownership of BLA 761029 was transferred to Biogen Idec.
- 08/20/2015: Major amendment acknowledgment letter was sent to the applicant; PDUFA goal date extended by 3 months to May 27, 2016.
- 08/24/2015: During the mid-cycle communication teleconference, the Applicant was informed that the Agency continues to evaluate whether a REMS would be necessary
- 02/24/2016: During the late-cycle communication teleconference the Applicant was informed that discussion of risk management options is continuing and a decision would be communicated shortly.
- 03/08/2016: REMS Oversight Committee (ROC) meeting. Recommendations by the ROC included a REMS with ETASU, including a REMS registry, were necessary for the approval of daclizumab.
- 03/11/2016: DRISK and DNP held an internal meeting where agreement was reached on the potential goals and the required elements for the REMS.
- 03/16/2016: Biogen was informed during a teleconference with DNP and DRISK that a REMS with ETASU is required.
- 03/30/2016: The Agency sent Biogen an outline of a generic draft REMS document in an Information Request.
- 04/08/2016: Biogen sent a draft REMS document via email.
- 04/12/2016: Biogen sent draft versions of the prescriber enrollment form, pharmacy enrollment form, patient enrollment form, and patient status form via email.
- 04/13/2016: DRISK and DNP held a teleconference with Biogen to discuss various aspects of the REMS. Topics discussed included the definition of the risks; the communication plan; use of the Medication Guide as the patient counseling tool; prescription limits;

baseline testing; the patient status form; the timing for on-line availability of REMS components; and the name of the REMS program.

- 04/15/2016: Biogen amended the REMS document in response to the Agency's comments and sent the draft and comments via email.
- 04/20/2016: The Agency sent Biogen a red-lined draft REMS document via email.
- 04/21/2016: DRISK and DNP held a teleconference with Biogen to discuss various aspects of the REMS. Topics discussed included the goals of the REMS; use of the patient enrollment form as the initial prescription; delegation of the prescriber monitoring and evaluation responsibilities; procurement of daclizumab by inpatient pharmacies and closed healthcare systems; mechanisms of enrollment; collection and storage of data for the registry; and the plan for auditing distributors and pharmacies.
- 04/29/2016: Biogen sent an amended draft REMS document and a draft REMS supporting document via email.
- 05/02/2016: Biogen sent draft versions of the patient enrollment form, patient status form, pharmacy enrollment form, and prescriber enrollment form via email.
- 05/05/2016: The Agency sent Biogen comments and redlined versions of the patient enrollment form, patient status form, pharmacy enrollment form, prescriber enrollment form, and REMS supporting document in an Information Request.
- 05/12/2016: The Agency sent Biogen redlined versions of the attestation statements for the patient enrollment form, pharmacy enrollment form, and prescriber enrollment form via email.
- 05/13/2016: Biogen sent comments and revised versions of the patient status form, patient enrollment form, pharmacy enrollment form, prescriber enrollment form, and REMS supporting document, and comments on the REMS website, via email.
- 05/18/2016: DRISK and DNP held a teleconference with Biogen to discuss various aspects of the REMS. Topics discussed included the patient status form categorization of adverse events; the REMS website; the goals of the REMS; the proposed process for delivering daclizumab to inpatient pharmacies; and the proposed auditing schedule of distributors and pharmacies.
- 05/19/2016: Biogen sent draft versions of the REMS overview, prescriber training, prescriber knowledge assessment, and REMS website via email.
- 05/20/2016: Biogen sent draft versions of the patient guide and patient wallet card; a revised version of the patient status form; and clarifying comments about the processes for delivery of daclizumab to inpatient pharmacies and the audit plan for certified pharmacies via email.

- 05/23/2016: The Agency sent Biogen redlined versions of the REMS assessment plan; REMS program overview; prescriber training; prescriber knowledge assessment; patient guide; patient wallet card; patient status form; and REMS website via email.
- 05/24/2016: DRISK and DNP held a teleconference with Biogen to discuss various aspects of the REMS. Topics discussed included the process for delivering daclizumab to inpatient pharmacies; the patient status form categorization of adverse events; and the REMS assessment plan.
- 05/24/2016: The Agency sent Biogen redlined versions of the REMS document; attestation statements for the patient enrollment form, pharmacy enrollment form, and prescriber enrollment form; patient status form; prescriber enrollment form; pharmacy enrollment form; and patient enrollment form via email.
- 05/25/2016: Biogen sent comments and revised versions of the REMS program overview; pharmacy enrollment form; prescriber enrollment form; patient enrollment form; patient wallet card; patient guide; prescriber knowledge assessment; and REMS website via email.
- 05/25/2016: DRISK and DNP held a teleconference with Biogen to discuss various aspects of the REMS. Topics discussed included the REMS document; attestation statements on the prescriber enrollment form; attestation statements on the patient enrollment form; and the assessment plan.
- 05/26/2016: The Agency sent Biogen comments on the REMS document; REMS supporting document; the patient guide; the REMS website; and the prescriber training via email.
- 05/26/2016: Biogen sent a draft version of the REMS Letter for healthcare providers and revised versions of the REMS document; REMS supporting document; REMS program overview; prescriber training; prescriber enrollment form; prescriber knowledge assessment; patient enrollment form; patient status form; patient guide; patient wallet card; pharmacy enrollment form; and REMS website via email.
- 05/26/2016: DRISK and DNP held a teleconference with Biogen to discuss the REMS document and the enrollment forms.
- 05/26/2016: The Agency sent Biogen comments on the REMS Letter for healthcare providers; patient enrollment form; prescriber enrollment form; and the assessment plan via email.
- 05/27/2016: Biogen sent a revised version of the REMS Letter for healthcare providers via email.
- 05/27/2016: Biogen submitted by email a REMS amendment to BLA 761029 that included an amended REMS document, appended materials, and supporting document.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION³⁻⁶

Multiple sclerosis is a chronic neurodegenerative disorder of the central nervous system with variable clinical and pathologic features. Inflammation, demyelination, and axon degeneration are the major pathologic mechanisms that cause the clinical manifestations, which commonly include sensory disturbances, visual loss, motor weakness, diplopia, gait disturbance, balance problems, and other symptoms.⁷ The cause of MS remains unknown. The most widely accepted theory is that MS begins as an inflammatory autoimmune disorder mediated by autoreactive lymphocytes.

Multiple sclerosis affects approximately 2.5 million people worldwide and is the most common cause of neurological disability among young adults. It is usually diagnosed between the ages of 20 to 40 years, with twice as many women affected as men. In December 2000, the raw prevalence of MS was determined to be 177 per 100,000 in Olmsted County, Minnesota. The use of this rate and the U.S. Census Bureau estimated population⁸ of 323 million people (as of April 2016) allow one to estimate that the U.S. prevalence of MS may be greater than 500,000 persons.⁹

Relapsing multiple sclerosis (RMS) is characterized by clearly defined relapses with either full recovery or clinical sequelae and residual disability upon recovery. There is no progression or minimal disease progression during the periods between disease relapses. This type of MS accounts for approximately 85 to 90 percent of MS cases at onset. However, most patients with RMS eventually enter a secondary progressive phase. Secondary progressive multiple sclerosis (SPMS) is characterized by an initial relapsing-remitting disease course followed by progression with or without occasional relapses. Some studies suggest that SPMS ultimately develops in most patients with RMS, and is the stage in which patients accumulate the greatest amount of neurologic disability.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS¹⁰

A number of immunomodulatory agents, including various preparations of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, dimethyl fumarate, teriflunomide, and fingolimod,

³ Olek MJ and Mowry E, 2016, Pathogenesis and epidemiology of multiple sclerosis. In:UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.

⁴ AbbVie Inc. Daclizumab, BLA 761029, received February 27, 2015, Section 2.5, Clinical Overview.

⁵ Olek MJ, 2016, Clinical course and classification of multiple sclerosis. In:UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.

⁶ Mayr WT, et al, 2003, Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985–2000. *Neurology*, 61:1373–1377.

⁷ FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

⁸ United States Census Bureau Population Clock (accessible at <http://www.census.gov>).

⁹ FDAAA factor (A): The estimated size of the population likely to use the drug involved.

¹⁰ Olek MJ, 2016, Disease-modifying treatments of relapsing-remitting multiple sclerosis in adults. In:UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.

are approved treatments for patients with RMS. These disease-modifying treatments reduce the relapse rate and improve brain MRI measures of MS disease activity.

Interferon beta therapies and glatiramer acetate require either intramuscular (IM) or SC injections. Although these treatments have established safety and efficacy profiles, many patients continue to experience disease activity while on therapy. Dimethyl fumarate, fingolimod, and teriflunomide are oral agents that offer a convenient route of administration. However, the oral therapies have been associated with clinically significant side effects, such as decreased lymphocyte counts for dimethyl fumarate; hepatotoxicity and lymphopenia with teriflunomide; and bradycardia, atrioventricular block, and potentially fatal varicella-zoster virus infections for fingolimod. Infusion therapy with natalizumab is recommended for patients with more active disease, though natalizumab is associated with the serious and potentially fatal risk of progressive multifocal leukoencephalopathy. Alemtuzumab has been shown to be more effective than interferon beta but has an increased risk of potentially serious infections and autoimmune disorders, including immune thrombocytopenia, and is indicated only for patients who have had an inadequate response to two or more MS therapies.

Mitoxantrone is a chemotherapeutic agent also indicated for worsening RMS but is associated with significant risks, including cardiotoxicity and leukemia. Mitoxantrone is usually reserved for patients with rapidly advancing disease who have failed other therapies.

Table 1 below shows the immunomodulatory treatments currently approved for relapsing MS and includes the hepatotoxicity labeling, labeling related to autoimmune disorders, and the risks and elements of any REMS approved to mitigate the associated risks of the product.

Table 1. Immunomodulatory agents for the treatment of relapsing multiple sclerosis

Drug (Date Approved)	Hepatotoxicity Labeling	Autoimmune Disorders Labeling	Type of REMS Risk(s) the REMS is to mitigate
Avonex (1996) (interferon beta-1a) Rebif (2002) (interferon beta-1a) Plegridy (2014) (peginterferon beta-1a)	WARNING Severe hepatic injury, including rare cases of hepatic failure, has been reported. Monitor patients for signs of hepatic injury.	WARNING [Avonex, Plegridy] Postmarketing reports of autoimmune disorders of multiple target organs included ITP, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis.	No REMS
Copaxone (1996) (glatiramer acetate)	<u>Postmarketing experience</u> Liver function abnormality, liver damage, hepatitis, cirrhosis of the liver		No REMS
Tysabri (2004) (natalizumab)	WARNING Clinically significant liver injury, including acute liver failure, reported in the postmarketing setting.		Medication Guide Elements to Assure Safe Use Progressive multifocal leukoencephalopathy
Gilenya (2010) (fingolimod)	WARNING Elevations of liver enzymes may occur. Liver enzymes should be monitored in patients who develop symptoms.		Communication Plan Bradycardia and atrioventricular block, infections, macular edema, posterior reversible encephalopathy syndrome, respiratory effects, liver injury , and fetal risk.
Aubagio (2012) (teriflunomide)	BOXED WARNING Severe liver injury including fatal liver failure in patients treated with leflunomide. Monitor ALT levels monthly for 6 months.		No REMS
Tecfidera (2013) (dimethyl fumarate)	<u>Adverse Reactions</u> Increased incidence of elevations of hepatic transaminases (<3xULN) seen in first 6 months of treatment.		No REMS
Lemtrada (2014) (alemtuzumab)		BOXED WARNING Serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Monitor complete blood counts with differential and renal function at periodic intervals for 48 months after the last dose.	Communication Plan Elements to Assure Safe Use Autoimmune conditions, infusion reactions, malignancies.

4 Benefit Assessment¹¹

Efficacy and safety of daclizumab were evaluated in two pivotal clinical studies. Study 201 was a randomized, double-blind, placebo-controlled, dose-ranging study conducted in 621 RMS patients that compared two different doses of daclizumab (150 mg SC every 4 weeks and 300 mg SC every 4 weeks) over a 1-year treatment period. Study 301 was a randomized, double-blind, active-control study comparing daclizumab 150 mg SC every 4 weeks to weekly IM injections of interferon beta-1a 30 mcg in 1,841 RMS patients over a two to three year (96 to 144 weeks) treatment period.

Key efficacy endpoints were primarily based on Study 301 because two years of treatment is generally required to support a finding of relevant and sustained clinical benefit. The primary efficacy endpoint of both Study 201 and Study 301 was the annualized relapse rate. Several supporting MRI and clinical endpoints were assessed in Study 301, including the number of new or enlarging T2 lesions on MRI over 96 weeks (which estimates the cumulative number of new brain lesions that have formed), the proportion of patients with progression of disability sustained for 12 weeks, the proportion of patients who were free of any relapse, as well as other endpoints. A very brief summary of the Agency's evaluation of the applicant's submission is described below.¹²

In Study 201, patients randomized to daclizumab 150 mg and 300 mg had a lower annualized relapse rate (0.211 and 0.230, respectively) relative to placebo-treated patients (0.458), which provided rate reductions of 54% in the daclizumab 150 mg group ($p < 0.0001$) and 50% in the daclizumab 300 mg group ($p = 0.0002$) compared with placebo. In Study 301, the annualized relapse rate was 0.216 in the daclizumab 150 mg group compared with 0.393 in the interferon beta-1a group, a reduction in relapse rate of approximately 45% ($p < 0.0001$). Daclizumab significantly reduced the mean number of new or newly enlarging T2 lesions at week 96 by 54% compared with interferon beta-1a (4.31 for daclizumab vs. 9.44 for interferon beta-1a). The estimated proportion of patients with sustained disability progression for 12 weeks was numerically less in the daclizumab group (16%) compared with the interferon beta-1a group (20%), but was not statistically significant. There was also a significant delay in the time to first relapse (which was used to calculate the proportion of relapse-free patients) in the group treated with daclizumab compared to interferon beta-1a.¹³

¹¹ FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

¹² Rodichok, L. Division of Neurology Drug Products. Clinical Review for Daclizumab HYP, BLA 761029, dated May 4, 2016.

¹³ Ling, X. Division of Biometrics I. Statistical Review and Evaluation of Daclizumab, BLA 761029, March 18, 2016.

5 Risk Assessment & Safe Use Conditions¹⁴

The safety population included data on a total of 2,236 patients who received daclizumab 150 mg or 300 mg in the controlled studies and their extensions, and a clinical pharmacology study and its extension. Serious adverse events (SAE),¹⁵ excluding MS/MS relapse events, were reported in 8.7% of the daclizumab 300 mg group, 7.2% of the daclizumab 150 mg group, and 5.9% of the placebo group in Study 201; a higher incidence of such events was seen in the daclizumab 150 mg group (15.5%) compared with the interferon beta-1a group (9.4%) in Study 301. The most important adverse events associated with the use of daclizumab appear to be hepatic injury, autoimmune diseases and other immune-mediated conditions, and cutaneous reactions.

All adverse events were assessed by the clinical investigators for severity (i.e., mild, moderate, or severe). The incidence of subjects with severe adverse events in Study 201 was 3% in the placebo group, 4% in the daclizumab 150 mg group, and 6% in the daclizumab 300 mg group; in Study 301, the incidence of adverse events assessed as severe, excluding MS/MS relapse events, was 12.6% in the daclizumab group and 10% in the interferon beta-1a group.

There were five deaths that occurred in daclizumab-treated patients. One patient died of liver failure due to autoimmune hepatitis. Another patient died after she experienced a serious cutaneous reaction that was complicated with sepsis, ischemic colitis, and an abscess of the psoas muscle. Two patients died after developing complications of aspiration pneumonia and sepsis in association with MS disease progression. The fifth patient (who was on anticoagulation therapy for a prior venous thrombosis) died of a traumatic brain hemorrhage after a fall at home that resulted in a subdural hematoma.

5.1 HEPATIC INJURY

OSE reviewed the risks of hepatic injury for this BLA.¹⁶ OSE determined that a consistently higher percentage of treatment-associated serum transaminase elevations (> 5x, 10x, and 20x the upper limit of normal) was observed in patients who received daclizumab compared with interferon beta-1a in the active controlled clinical study as well as in the placebo-controlled study. Serious drug-induced liver injury occurred in 20 patients in the daclizumab safety population, including four Hy's law cases. Although some cases were confounded by other hepatotoxic drugs, seven of

¹⁴ Villalba L. Division of Neurology Drug Products. Clinical Review for Daclizumab HYP, BLA 761029, March 24, 2016.

¹⁵ Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

¹⁶ Avigan, M. Office of Surveillance and Epidemiology. Hepatology Review for Daclizumab HYP, BLA 761029, dated November 9, 2015.

the 20 cases were marked by unique autoimmune features. Many of the daclizumab associated liver injury cases were not associated with high titers of serum ANA or other autoantibodies as is typically seen in idiopathic AIH. The rate of autoimmune hepatitis in the daclizumab clinical studies was 134/100,000 person-years, whereas the background rate in the untreated MS population is 24/100,000 person-years.¹⁷ One case of autoimmune hepatitis, which occurred in a double-blind extension of Study 201, resulted in fulminant liver failure and death of the patient. Following this event, all ongoing study protocols were updated to include liver function testing every four weeks during treatment, and guidelines for suspension and discontinuation of daclizumab were added. Furthermore, the protocols were updated to limit concomitant treatment with specific medications associated with hepatotoxicity and to test transaminases within seven days prior to dosing. Other cases of autoimmune hepatitis were clinically severe, with elevations of serum transaminase levels, bilirubin, and other symptoms, and required treatment with corticosteroids and immunosuppressive agents such as azathioprine; some patients required treatment with immunosuppressants three years after the last dose of daclizumab. Although there was variability in the time to onset and clinical severity, many liver injuries occurred after long periods of continuous treatment until the onset of hepatitis, and some events only appeared a few months after treatment discontinuation.

5.2 ADDITIONAL IMMUNE-MEDIATED EVENTS

In addition to autoimmune hepatitis, various other immune-mediated adverse events were also reported including non-infectious colitis (n=28), sarcoidosis (n=9), celiac disease (n=4), interstitial lung disease (n=5), and other conditions such as diabetes mellitus and thyroid disease. Some patients presented with concurrent or sequential immune related conditions. There was an imbalance of non-infectious colitis-related adverse events on daclizumab 150 mg (n=14) compared with no cases in the interferon beta-1a arm in Study 301. Some immune-mediated reactions required hospitalizations, invasive procedures, and prolonged treatment with immunosuppressive therapy.

Lymphadenopathy, which included lymphadenitis or lymphoid tissue hyperplasia, developed in approximately 6% of patients (n=137) in the safety population, of which 0.8% of the adverse events were considered serious. The rate of lymphadenopathy in Study 301 was 5% on daclizumab compared with 0.8% on interferon beta-1a.

5.3 CUTANEOUS REACTIONS

Cutaneous reactions occurred in 40% of all patients exposed to daclizumab, of which 13% were serious, severe, or led to drug withdrawal. The scope of reactions included eczema, psoriasis, cutaneous vasculitis, cutaneous sarcoidosis, and other severe drug reactions, including three cases consistent with drug reaction with eosinophilia and systemic symptoms (DRESS). Some patients

¹⁷ FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

required hospitalization, the use of topical tacrolimus or systemic corticosteroids, or plasmapheresis. The time to resolution in some cases required months. In Study 301, cutaneous reactions were more frequent in the daclizumab 150 mg group compared with interferon beta-1a (37% vs. 19%, respectively) for the overall number of adverse events. Serious skin reactions occurred in 2% of subjects treated with daclizumab and 0.1% of patients who received interferon beta-1a.

6 Analysis of Expected Postmarket Use

Based on its safety profile, the use of daclizumab will be indicated for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS (similarly to Lemtrada). For this reason, we anticipate that the likely prescribers of daclizumab will be neurologists in MS specialty care centers who have experience with MS drugs that have severe toxicities and serious adverse events. The dispensing of daclizumab, which will be packaged as a single-dose pre-filled syringe for subcutaneous injection, could be performed by any outpatient or inpatient pharmacy and it is expected that this product would be self-administered by patients or administered to patients by caregivers in the home setting.

Prescribers will have an important role in managing the risk of daclizumab-induced liver injury and immune mediated conditions through monthly monitoring and evaluation. Although the current data suggests that the risk of autoimmune adverse events cannot be predicted in a given patient, the potential for rapid acceleration of organ injury in some patients makes adherence with regular assessments and monthly monitoring important. We expect that this monitoring may improve patient outcomes in those cases where autoimmune reactions develop by increasing opportunities for early recognition, diagnosis, and appropriate intervention if liver injury or other immune mediated adverse events are detected.

As daclizumab will mainly be an outpatient use product that is likely to be administered by patients or caregivers at home, we expect patients will follow-up with the prescribing neurologist every three to six months. If patients are tolerating and responding well to their treatment, their compliance with monthly monitoring in between the follow-up appointments with the neurologist may be expected to be reduced.

7 Discussion of Need for a REMS

The risks of hepatotoxicity and autoimmune disorders associated with daclizumab are serious as demonstrated by the trial data. Twenty patients in the safety population experienced serious drug-induced liver injury, including four Hy's law cases. Seven cases of drug-induced liver injury showed autoimmune features. Liver injury (some characterized by rapid acceleration of organ injury) was not predictable and occurred at any time during treatment as well as for a period of time after discontinuation of treatment, resulting in serious outcomes including hospitalization, clinically

severe reactions, and death. During the clinical studies, the protocols were updated to include liver function testing every four weeks throughout the study, and guidelines for suspension and discontinuation of daclizumab were added. The protocols were also updated to limit concomitant treatments associated with hepatotoxicity and to test transaminases within seven days prior to dosing. Additional serious autoimmune conditions occurred in patients treated with daclizumab, including non-infectious colitis, sarcoidosis, and cutaneous reactions, among other conditions. Some patients required hospitalization, invasive procedures, or treatment interventions with systemic corticosteroids or immunosuppressants for these conditions.

Clinical assessments and monthly monitoring as could be established in a REMS would be expected to help reduce the risk of serious outcomes, if patients and prescribers adhere to monitoring and evaluation, and appropriate treatment interventions are made in a timely manner. Such assessments and monitoring could reflect the protocol changes implemented in the trials. Patients who are candidates for daclizumab will likely have a high willingness to accept risk given the severity of the disease and the general toxicities of the other therapies, but an educational program about the serious risks and monitoring requirements is important for the purpose of allowing patients to make informed decisions and encouraging monitoring compliance, as well as to receive education regarding the signs and symptoms of the serious risks associated with daclizumab, should they occur. In addition, reliable information about the long-term safety of daclizumab in the treatment of MS is important to obtain in the post-market setting for the purpose of determining the incidence rates of serious daclizumab-induced adverse events and clinical attributes that are risk factors or protective factors for those events. This can be accomplished by a REMS patient registry in which all treated patients would be enrolled and monitored during treatment and for a certain period of time after the end of treatment.

Several of the approved immunomodulatory agents for the treatment of MS are associated with hepatotoxicity, as shown above in Table 1 above. For most of these agents, the characteristics of the hepatic risk in context may only partly overlap with that for daclizumab. For example, the incidence of hepatotoxicity with interferon beta-1a and natalizumab appears to be much lower than with daclizumab. In the case of teriflunomide, the risk is largely based on hepatotoxicity concerns with the parent compound, leflunomide. Teriflunomide is the only approved MS treatment with a Boxed Warning for severe liver injury that recommends monthly testing of liver function, but such testing is only recommended for the first six months of therapy. In contrast, daclizumab will require monthly monitoring of liver function throughout the course of treatment and for six months after the last dose in order to include a sufficient elapse of time to allow for recovery of immune cells. In this way, the autoimmune risks with daclizumab present in a manner that is more similar to alemtuzumab, which is approved with a narrow MS indication based on safety concerns and requires a REMS with ETASU for long-term periodic monitoring of serious autoimmune injuries.

Various risk management options for daclizumab-induced liver injury were discussed at a meeting of the REMS Oversight Committee (ROC), which recommended that a REMS with ETASU is

required to mitigate the risks of hepatotoxicity. Additionally, it was decided upon by the review team that the risks of immune mediated disorders associated with daclizumab are serious and should also be included in the REMS.

The healthcare community and system have experience with ETASU REMS programs for the treatment of MS (Lemtrada, Tysabri) that have established processes for monitoring and safe use. Therefore, the introduction of a REMS with ETASU for daclizumab should be able to be integrated practice and systems.

8 Risk Management Activities Proposed by the Applicant

In the initial BLA submission, the Applicant proposed a REMS comprised of a Medication Guide, communication plan, and a timetable for submission of assessments, to mitigate the risk of severe hepatic injury. The REMS proposal was amended after the Agency informed Biogen that a REMS with ETASU is required, to mitigate the risks of severe and fatal hepatic injury and serious immune mediated disorders. The following sections of this review address Biogen's amended REMS proposal submitted May 26, 2016.

8.1 REVIEW OF APPLICANT'S PROPOSED REMS

8.1.1 REMS Goals

The Agency provided Biogen a draft REMS document on March 30, 2016 that proposed goals to mitigate the risks of severe and fatal hepatic injury and serious autoimmune disorders associated with daclizumab by:

- Helping to ensure informed decisions about the safe use of daclizumab by:
 - Informing patients about the risks of severe and fatal hepatic injury and serious autoimmune disorders associated with daclizumab and the need for baseline and monthly monitoring; and
 - Informing healthcare providers about the risks of severe and fatal hepatic injury and serious autoimmune disorders associated with daclizumab, the need to counsel patients, and the need for baseline and monthly monitoring and evaluation.
- Helping to ensure the safe use of daclizumab by:
 - Ensuring that only certified prescribers prescribe daclizumab
 - Ensuring that daclizumab is dispensed only by certified pharmacies
 - Ensuring that only enrolled patients receive daclizumab
 - Ensuring that certified prescribers submit documentation of monitoring and evaluation of patients who receive daclizumab
 - Ensuring that every patient that receives daclizumab is enrolled in a registry

Reviewer comment: After further internal discussion, it was determined the goals should be revised to more accurately reflect current Agency thinking on formatting of REMS goals and better align the REMS goals and objectives. These revisions were discussed with Biogen during two subsequent teleconferences. The applicant's amended REMS submission proposed goals that align with the Agency's goals are as follows:

To mitigate the risks of severe and fatal hepatic injury and serious immune mediated disorders associated with daclizumab by:

- ensuring that prescribers are educated on the following:
 - the potential risks of severe and fatal hepatic injury and serious immune mediated disorders associated with the use of daclizumab
 - the need to counsel patients about these risks and the need for appropriate baseline and monthly monitoring
- ensuring that prescribers are educated on and adhere to:
 - required baseline and monthly monitoring and evaluation of patients who receive daclizumab
- ensuring that patients are informed about:
 - the potential risks of severe and fatal hepatic injury and serious immune mediated disorders associated with the use of daclizumab
 - appropriate baseline and monthly monitoring
- enrollment of all patients in a registry to further support long-term safety and safe use of daclizumab

Reviewer comment: We agree with the proposed goals and objectives of the REMS.

8.1.2 REMS Elements

Communication plan

A communication plan that includes a REMS Program Letter to Healthcare Providers is needed to support implementation of the ETASU program. Hard copy letters will be sent within 60 calendar days of the approval of the REMS and Biogen must send a second mailing at 12 and 24 months from the date of the REMS approval. The intended audience for the letter must be prescribers who have written at least one prescription within the previous 2 years for a prescription drug indicated for the treatment of multiple sclerosis.

During a discussion of the REMS by teleconference, Biogen disagreed with the need to monitor receipt of the letters or the need to follow-up by email for mailed letters that are undeliverable and returned (these tracking activities had been proposed by DRISK). The Applicant subsequently agreed to send an email one time within 10 business days after the letter is returned for those healthcare providers for whom an email address is available.

Reviewer comments: The subsequent proposal by Biogen to send a one-time email for returned letters, when the email address is available, is acceptable.

- **REMS Program Letter for Healthcare Providers**

The REMS Program Letter for Healthcare Providers informs healthcare providers of the risks addressed by the REMS, requirements for healthcare provider training, and the importance of adverse event reporting.

Reviewer comments: DRISK concurs with Biogen's REMS Program Letter for Healthcare Providers.

Prescriber certification (ETASU A)

Prescribers of daclizumab will be required to be specially certified. To become certified, a prescriber must complete training (including a knowledge assessment) and enroll in the REMS. The purpose of the training materials is to inform prescribers about the risks of severe and fatal hepatic injury and serious immune mediated disorders associated with daclizumab. In addition, prescribers will be informed as to the requirements for baseline and monthly liver function testing, evaluation of the results, recommendations for appropriate management of the patient, and REMS program operations. Prescribers will need to successfully complete a knowledge assessment in order to receive certification.

Prescribers will need to enroll patients into the REMS and registry program and provide them with counseling and educational materials related to the risks, monitoring requirements, and that the patient's consent to participate in the registry is needed to receive daclizumab. Prescribers will attest that baseline lab values will be completed and evaluated prior to the patient's first dose using the patient enrollment form. Prescribers will also attest that monthly monitoring and evaluation was completed through the use of a patient status form that will be submitted to the REMS program every 90 days. Although prescribers may utilize delegates to complete the patient status form on their behalf, the certified prescriber remains responsible for compliance with all program requirements for monitoring and evaluation of the patient. Patients will no longer be authorized for further dispensing of the drug if the status form is not received within ^(b)₍₄₎ days of the due date, to prevent ongoing therapy in the absence of monitoring. If the status form is not received after an additional ^(b)₍₄₎ days, Biogen will begin procedures to de-enroll the patient from the REMS.

REMS Materials that Support Prescriber Certification

The following materials support prescriber training, enrollment, and certification regarding their responsibilities under the REMS:

- **REMS Program Overview**

The REMS Program Overview is a quick reference tool that provides information to prescribers and pharmacies about the program requirements for enrollment of prescribers, pharmacies, and patients,

and where to find additional REMS program information and resources. It is included in the REMS to introduce prescribers and pharmacies to the purpose of the REMS, how the program operates, and the different requirements for each stakeholder.

Reviewer comments: DRISK concurs with Biogen's REMS Program Overview.

- REMS Program Prescriber Training

The prescriber training requires prescribers to review the physician education slide deck and to successfully complete a knowledge assessment. The purpose of the prescriber training is to reinforce the information contained in the prescribing information about the serious risks, including recommendations for appropriate management of the patient that are consistent with labeling, and to educate the prescriber as to the REMS program requirements. The REMS program requirements for prescribers include self-enrollment, enrollment of patients, attestation to perform the necessary monitoring requirements, counseling patients using the patient counseling guide, providing patients with a wallet card, and completion of a patient status form every 90 days during treatment and every 90 days for 6 months after discontinuation of the drug.

Reviewer comments: DRISK concurs with Biogen's REMS Program Prescriber Training.

- REMS Program Prescriber Enrollment Form

The prescriber enrollment form collects information about the prescriber and their medical practice and includes detailed language where the prescriber attests to completion of the certification requirements and acknowledges their responsibilities under the program.

Reviewer comments: Biogen proposed to include (b) (4) We disagreed with making this a requirement under the REMS because (b) (4) is not necessary to mitigate the risks. After discussion with Biogen during a teleconference, they agreed to remove the (b) (4). Biogen also proposed (b) (4) (b) (4). We disagreed with the need (b) (4). Biogen subsequently removed (b) (4).

DRISK concurs with Biogen's REMS Program Prescriber Enrollment Form.

- REMS Program Prescriber Knowledge Assessment

The prescriber knowledge assessment is to be completed after the prescriber has reviewed the program training materials. The successful completion of a knowledge assessment is a prerequisite for prescriber certification and will help to ensure adequate understanding of the risks and program requirements. (b) (4)

Reviewer comments: DRISK concurs with Biogen's REMS Program Prescriber Knowledge Assessment.

- REMS Program Patient Enrollment Form

Patients starting daclizumab must be enrolled in the REMS program by a certified prescriber. The purpose of the patient enrollment form is to help ensure patients have received and read the patient guide, received counseling from the prescriber regarding the risks and monitoring requirements, and have received the patient wallet card. The patient enrollment form collects identifying information and includes detailed language where the patient acknowledges their understanding of the risks and their responsibilities under the program, including that they will need to comply with the required monthly monitoring to receive daclizumab.

Reviewer comments: DRISK concurs with Biogen's REMS Program Patient Enrollment Form.

- REMS Program Patient Status Form

Certified prescribers must use the patient status form to document completion of required monthly monitoring and evaluation of patients. The form will also be used to report the occurrence of hepatic injury or immune mediated disorders that were not previously reported to the program. The REMS requires that patients are monitored and evaluated monthly, and that documentation of this activity is submitted to the program every 90 days while the patient is on therapy and for six months after discontinuation. The time of reference used for determining collection of the forms is based on the date of initial dispensing. Biogen will provide the patient status form to each certified prescriber for each enrolled patient in advance of the 90-day due date. If the form is not received within (b) (4) days of the due date, the patient will not be authorized for further dispensing of daclizumab, and if the form is not received within an additional (b) (4) days, Biogen will begin de-enrollment procedures for the patient.

Reviewer comments:

- *The timing of the prescriber's submission of the patient status form is 90 days after the date of initial dispensation and every 90 days thereafter while the patient is on therapy and for six months after discontinuation; this activity will be tracked by the Applicant. Biogen will provide each certified prescriber the form for each patient in advance of the due date.*
- *Biogen agreed with our request to delete (b) (4) from the categorization of hepatic and immune mediated adverse events on the patient status form as a means of enabling collection of a wider range of potential adverse events. Biogen's safety specialists will follow-up with the reporting prescriber to procure all necessary information to complete the report and all required data for the safety database.*

DRISK concurs with Biogen's REMS Program Patient Status Form.

- REMS Program Patient Guide

The prescriber is required to use the patient guide for counseling the patient upon initiating daclizumab. The guide is written in patient-friendly language and provides information related to the risks of treatment, signs and symptoms of adverse events for which to seek medical attention, and instructions about the required monitoring that patients must comply with in order to continue to receive the drug and should it be discontinued.

Reviewer comments: DRISK concurs with Biogen's REMS Program Patient Guide.

- REMS Program Patient Wallet Card

The patient wallet card is to be carried by the patient to serve as a reminder of the risks, signs and symptoms of adverse events for which to seek medical attention, and the monitoring requirements. It will also include the prescribing physician's contact information. The wallet card will also serve as a method of informing other physicians and caregivers who may be caring for the patient that the patient is taking daclizumab, the associated risks, and contact information for the prescribing physician.

Reviewer comments: DRISK concurs with Biogen's REMS Program Patient Wallet Card.

Pharmacy certification (ETASU B)

Daclizumab is expected to be used primarily in an outpatient setting, however from a safety perspective daclizumab could be dispensed by any certified outpatient or inpatient pharmacy because the product is typically self-administered at home. To obtain certification, pharmacies must enroll in the REMS by reviewing training materials and agreeing to dispense only to patients enrolled and authorized in the program, that have a prescription written by a prescriber enrolled in the program. Dispensing of daclizumab is limited to a one-month supply in order to avoid situations where patients could potentially continue treatment for a prolonged period of time without completing the corresponding monitoring. Integrated health systems such as Veterans Affairs, Department of Defense, and Kaiser will have the ability to become certified pharmacies in order to ensure appropriate access for patients. (b) (4)

(b) (4) Biogen proposed (b) (4)

(b) (4)

(b) (4)

Reviewer comments: (b) (4)

(b) (4) . DRISK (b) (4)

aligned with Biogen's approach (b) (4)

(b) (4) . DRISK will monitor the impact this may have (b) (4)

Biogen has added clarifying information to the REMS program overview and REMS website that advises pharmacies to contact Biogen for questions about how to obtain daclizumab (b) (4)

(b) (4)

(b) (4)

REMS Materials that Support Pharmacy Certification

- REMS Program Pharmacy Enrollment Form

The pharmacy enrollment form collects information about the pharmacy and its authorized representative and includes detailed language whereby the pharmacy acknowledges and agrees to its responsibilities under the program.

Reviewer comments: DRISK concurs with Biogen's REMS Program Pharmacy Enrollment Form.

- REMS Program Website

The REMS program website will contain the prescribing information and all appended REMS program materials. All of these materials will be available in a format that can be downloaded and printed from the website, and they can also be provided by contacting the REMS program call center.

The call center will be operational upon approval to answer program questions and the website will be operational within 60 days of REMS approval.

Reviewer comments: DRISK concurs with Biogen's REMS Program Website

Documentation of safe use conditions (ETASU D)

Documentation of safe use conditions is necessary to ensure that daclizumab is only dispensed to or administered to patients who have been enrolled in the REMS and who have received counseling from the prescriber about the risks and monitoring requirements. The primary purpose of the safe

¹⁸ Biogen asserted that only 8.5% of MS patients taking a therapy indicated for MS were hospitalized in 2014 for an average of 7.6 days per stay. Daclizumab is self-administered monthly and can be taken up to two weeks after a missed dose, therefore, the likelihood that a patient would require treatment with daclizumab while hospitalized is low. (Email communication from Biogen, May 20, 2016)

use conditions is to allow patients to make informed decisions regarding the acceptability of the risks and to agree to the REMS program requirements.

Patients will be subject to certain monitoring (ETASU E)

Prescribers will document that baseline and monthly monitoring requirements and evaluation were completed using the REMS Program Patient Status Form that will be submitted periodically to the REMS program. The Applicant will be required to send monthly reminders to all patients who have received daclizumab within the last 6 months to support their compliance with monitoring. Biogen will provide the patient status form to each certified prescriber for each enrolled patient in advance of the 90-day due date. It will be the applicant's responsibility to contact prescribers in the event of missing or late authorizations and to formulate processes to hold dispensing of product or to de-enroll patients and/or prescribers for non-adherence with the program requirements.

Each patient using daclizumab is enrolled in a registry (ETASU F)

To mitigate the risks of hepatotoxicity and autoimmune disorders and to obtain information about the long-term safety of daclizumab, including potential risk factors or protective factors for adverse events, all patients who receive daclizumab must consent to enroll in the REMS program and agree to be part of a patient registry. The primary objective of the registry is to: 1) ensure that only enrolled and authorized patients receive daclizumab, 2) to obtain information on the incidence of severe and fatal hepatic injury and serious immune mediated events, and (3) information that further supports long-term safety and safe use of daclizumab. Biogen will follow-up with the healthcare provider to procure all necessary information to complete reports on serious and fatal hepatic injury and serious immune mediated events.

Implementation System

The implementation system will address processes and procedures related to distribution and dispensing; the monitoring of compliance of distributors and certified entities with regard to dispensing, patient monitoring/evaluation, and corrective actions; the institution of a secure database of patients and prescribers enrolled in the REMS; the availability of a REMS program website and call center; and the institution of a monthly reminder system for enrolled patients who have had at least one prescription dispensed to them.

Reviewer comments: With regard to auditing of distributors and certified pharmacies, Biogen proposed [REDACTED] (b) (4) audits [REDACTED] (b) (4) based on internal procedures they use in another REMS program. After further negotiation by teleconference and email, Biogen agreed to audit 25% of certified pharmacies within 90 days of the first dose dispensed and to audit distributors within 180 days. Thereafter, Biogen will maintain an ongoing annual audit plan.

DRISK concurs with Biogen's Implementation System.

8.1.3 REMS Assessment Plan

Biogen will evaluate the effectiveness of the program to determine if the REMS is meeting its goals. REMS assessments will be submitted to the Agency at 6 months, one year, and annually thereafter from the date of approval of the REMS. Assessments will include program metrics; distribution data; knowledge and behavior surveys of prescribers and patients; adverse events; and metrics regarding the use of daclizumab at inpatient and institutional healthcare facilities.

8.1.4 REMS Materials and Key Risk Messages

Risk Messages for Healthcare Providers

Risk Message #1: Zinbryta can cause severe and fatal hepatic injury.

- Drug-related liver injury that can be life-threatening, including fatal autoimmune hepatitis, can occur with Zinbryta.

Prescribers must:

- Monitor and evaluate patients' liver tests at baseline, and monthly before giving the next dose of Zinbryta during Zinbryta treatment, and for 6 months after discontinuation

Risk Message #2: Zinbryta can cause serious immune mediated disorders.

- Immune disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders can occur with Zinbryta
 - Prescribers should be vigilant regarding emergent immune-mediated disorders and monitor for signs and symptoms.

Healthcare providers must be specially certified in order to prescribe Zinbryta. To become certified, a prescriber must complete training (*including a knowledge assessment*) and enroll him/her and their patient in the REMS Program.

Prescribers must complete training using the *Zinbryta REMS Program Overview*, and *Zinbryta REMS Program Prescriber Training*

Prescribers must use the *Zinbryta REMS Program Patient Guide* to counsel patients about:

- Drug related liver injury, that can be life-threatening, including fatal autoimmune hepatitis
- Immune disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders

Prescribers must report any adverse events suggestive of hepatic injury and immune mediated disorders to the Zinbryta REMS Program. To report adverse events, prescribers can either call the Zinbryta REMS Program directly or use the reporting section of the *Zinbryta REMS Program Patient Status Form*.

Risk Message #3: Pharmacies must be certified in order to dispense Zinbryta.

To become certified, pharmacies must enroll in the Zinbryta REMS Program by reviewing Zinbryta REMS Program Overview and agreeing to dispense drug only to patients enrolled and authorized in the program, that have a prescription written by a prescriber enrolled in the Program.

Risk Messages for Patients

Risk Message #1: There are serious risks associated with Zinbryta, including:

- **Liver problems**
 - (b) (4) nausea (feeling sick to your stomach)
 - Vomiting
 - Stomach pain
 - Worsening fatigue
 - Loss of appetite (b) (4)
 - Your skin or the whites of your eyes turn yellow
 - Dark urine
- **Immune reactions**
 - Skin reactions such as rash or skin irritation
 - Tender, painful, or swollen lymph nodes
 - Intestinal problems (colitis). Symptoms can include fever, stomach pain, blood in your stools, or diarrhea that does not go away
 - Any new and unexplained symptoms of any part of the body

Risk Message #2: Patients must complete appropriate baseline and monthly monitoring; while on treatment and for 6 months following discontinuation of treatment. The Zinbryta REMS Program Patient Guide and Wallet Card will assist patients in completing the required monitoring.

9 Conclusion & Recommendations

DRISK finds the proposed REMS for daclizumab and its appended materials (attached), and the supporting document, as submitted on May 27, 2016 (submitted by email), are acceptable. DRISK recommends approval of the REMS appended to this review.

The following assessment plan is to be included in the approval letter:

- 1) REMS Program Utilization Statistics
 - a) Patients
 - i) Number of newly enrolled and active* (existing) patients
 - ii) Number of patients who have discontinued therapy
 - b) Prescribers
 - i) Number of newly enrolled and active* (existing) certified prescribers

- c) Pharmacies
 - i) Number of newly enrolled and active* (existing) certified pharmacies
- 2) REMS Program Infrastructure and Performance
 - a) Percent of prescriber responses attesting to patient compliance with required monitoring
 - b) Percent of patients whose physician attested as being compliant with the required monitoring
 - c) Number of patients not enrolled in the REMS program/ registry who were dispensed medication
 - d) Number of enrolled patients who were not authorized in the REMS program who were dispensed medication
 - e) Number of pharmacies who dispensed drug to non-authorized patients
 - f) Number of Zinbryta REMS Program patient status forms received within 25 days of the due date (day 115)
 - g) Number of Zinbryta REMS Program patient status forms not received within 25 days (day 115) of the due date
 - h) Number of Zinbryta REMS Program patient status forms not received within 55 days (day 145) of the due date and resulting patient de-enrollments
 - i) From audited pharmacies only, provide the number of Zinbryta shipments sent to patients during the time authorization to dispense was lost
 - j) Number of Zinbryta REMS Program patient status forms outstanding at the end of the reporting period
 - k) Number of Zinbryta REMS Program patient status forms for discontinued patients submitted during the reporting period
 - l) Number of outstanding Zinbryta REMS Program patient status forms for discontinued patients during the reporting period
 - m) Number of certified prescribers that were decertified from the Zinbryta REMS program during the reporting period
 - n) Number of patients unenrolled from the Zinbryta REMS program during the reporting period due to noncompliance with REMS requirements
 - o) Number of certified pharmacies that were decertified from the Zinbryta REMS program during the reporting period due to noncompliance with REMS requirements
 - p) Number of non-certified pharmacies that received shipments during the assessment period
 - i) Number of shipments to institutional/inpatient healthcare facilities (including long term care, rehabilitation, skilled nursing facilities, nursing homes, etc.)
 - ii) Number of shipments to locations other than institutional/inpatient healthcare facilities (i.e. other non-certified retail, mail order or specialty pharmacies)
 - q) Number of patients receiving delivery of product at a healthcare facility from a certified pharmacy during the assessment period
 - i) Of the patients above, number that have an adverse event reported within 90 days of the shipment date
 - ii) Disposition of product to include date shipped, date received, date injected, or date returned to original shipping source, whenever possible
- 3) Knowledge (beginning with the 12-month assessment)
 - a) Patient understanding of serious risks and safe use conditions for Zinbryta

- b) Prescriber understanding of serious risks, safe use conditions, and proper patient selection for Zinbryta
- 4) Safety surveillance
- a) Number of Zinbryta REMS Program patient status forms that reported an event of severe or fatal hepatic injury or a serious immune mediated disorder and resulting prescription disposition (discontinued, continued)
 - b) Adverse event assessments of severe and fatal hepatic injury and serious immune mediated disorders
- 5) An assessment of the extent to which the elements to assure safe use of the REMS are meeting the goals of the REMS and whether the goals or elements should be modified

*For the purposes of the REMS assessment, active prescribers, pharmacies or patients are those that have prescribed, dispensed, or received at least one prescription for Zinbryta during the assessment period.

10 Materials Reviewed

1. Division of Neurology Products, Pre-BLA Meeting Minutes for Daclizumab, IND 12120, November 7, 2014.
2. AbbVie, Clinical Overview for Daclizumab, BLA 761029, February 27, 2015.
3. AbbVie, Summary of Clinical Safety for Daclizumab, BLA 761029, February 27, 2015.
4. AbbVie, Risk Evaluation and Mitigation Strategy for Daclizumab, BLA 761029, February 27, 2015.
5. Division of Neurology Products, Mid-cycle Meeting Clinical Slides, Daclizumab, BLA 761029, July 29, 2015.
6. Avigan, M., Office of Surveillance and Epidemiology. Hepatology Review for Daclizumab, BLA 761029, November 9, 2015.
7. Senior, J., Office of Surveillance and Epidemiology. Hepatology Review for Daclizumab, BLA 761029, January 18, 2016.
8. REMS Oversight Committee. Daclizumab Meeting Slides, March 8, 2016.
9. Biogen, European Union Risk Management Program for Daclizumab, BLA 761029, March 11, 2016.
10. Ling, X., Division of Biometrics I. Statistical Review and Evaluation of Daclizumab, BLA 761029, March 18, 2016.
11. Villalba L., Division of Neurology Drug Products. Clinical Safety Review for Daclizumab, BLA 761029, March 24, 2016.
12. Rodichok, L., Division of Neurology Drug Products. Clinical Efficacy Review for Daclizumab, BLA 761029, May 4, 2016.
13. Moukhtara, A., Office of Prescription Drug Promotion. Zinbryta (daclizumab), Comments on Draft REMS Materials, BLA 761029, May 25, 2016.

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/s/

ROBERT G PRATT
05/27/2016

CYNTHIA L LACIVITA
05/27/2016
Concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Neurology Products

NDA/BLA #s: BLA 761029
Products: Zinbryta (daclizumab) injection, for subcutaneous use, 150 mg/ml
APPLICANT: Biogen
FROM: Alice Hughes, M.D.
DATE: May 26, 2016

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Zinbryta (daclizumab) to ensure that the benefits of the drug outweigh the risks of severe and fatal hepatic injury and serious immune-mediated disorders. In reaching this determination, we considered the following:

- A. Zinbryta (daclizumab) will be approved for the treatment of patients with relapsing forms of multiple sclerosis (MS). A review of published studies determined that the median prevalence of MS in North America was 2.0/1,000 persons (range 1.7-2.3)¹. Because of its safety profile, the indication statement will state that use of Zinbryta should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. We do not have an estimate of the number of such patients who might be treated with Zinbryta (daclizumab).

¹ Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohammed M, Chaudhuri AR, Zalutsky R. How common are the “common” neurological disorders? *Neurology* 2007;68:326-337.

- B. MS is an immune-mediated neurodegenerative disorder that leads to physical disability. Onset is most commonly in early to middle adulthood, but pediatric onset is possible. MS patients may experience weakness of the limbs, impaired ability to walk, visual symptoms including decreased acuity and visual blurring, sensory symptoms including tingling, ataxia, bladder dysfunction, memory loss and impaired attention, depression, and fatigue. MS can rapidly evolve to an incapacitating disease requiring profound lifestyle adjustments.²
- C. A 2-year randomized, double-blind, active-controlled (Avonex, 30 mcg intramuscular, once weekly) trial was performed in patients with relapsing MS. The annualized relapse rate (primary endpoint) and number of new or newly enlarging T2 hyperintense lesions were significantly lower in patients treated with Zinbryta (daclizumab, 150 mg subcutaneously every 4 weeks) than in patients who received Avonex. There was no statistically significant effect on disability progression.

A 1-year randomized, double-blind, placebo-controlled study was performed in patients with relapsing MS. The annualized relapse rate (primary endpoint) was significantly lower in patients treated with Zinbryta (daclizumab, 150 mg subcutaneously every 4 weeks) than in patients who received placebo. The number of new and newly enlarging T2 lesions and proportion of patients with disability progression were significantly lower in patients treated with Zinbryta (daclizumab) than in patients who received placebo.

- D. The duration of therapy is expected to be chronic and potentially life-long.
- E. Zinbryta causes life-threatening severe liver injury, including liver failure and autoimmune hepatitis. Serious events of drug-induced liver injury occurred in 0.5% of 919 Zinbryta-treated patients compared to 0.1% of 922 Avonex-treated patients and in 0.7% of Zinbryta-treated patients compared to no events in placebo patients in controlled studies. Overall, serious events of liver injury occurred in 1% of 2236 Zinbryta-treated patients. Seven patients developed autoimmune hepatitis, including one fatal case that occurred in a patient re-initiating Zinbryta after a planned 6 month treatment interruption period. Hy's law cases occurred in 0.7% of 919 Zinbryta-treated patients compared to 0.1% of 922 Avonex treated patients.

Zinbryta increases the risk of immune-mediated disorders. Immune-mediated adverse reactions occurred in 28% of 2236 patients on Zinbryta in clinical trials. In the active-controlled study, immune-mediated conditions occurred in 32% of Zinbryta-treated patients compared with 12% for Avonex-treated patients. Serious immune-mediated conditions were observed in 4% of patients treated with Zinbryta compared with fewer than 1% of Avonex treated patients. In addition to autoimmune hepatitis, immune-mediated conditions included skin reactions, including dermatitis and eczema as well as psoriatic conditions, lymphadenopathy, and non-infectious colitis, as well as a variety of reactions affecting most organ systems. Some of these adverse

² Harrison's Principles of Internal Medicine-17th Ed. (2008)

reactions were systemic multi-organ inflammatory reactions. Anaphylaxis, angioedema, and urticaria also occurred.

In controlled trials, infections occurred in 50% of Zinbryta-treated patients compared to 44% of patients taking placebo and in 65% of Zinbryta-treated patients compared to 57% of Avonex treated patients. Serious infections occurred in 3% of Zinbryta-treated patients compared to none in placebo-treated patients and in 4% of Zinbryta-treated patients compared to 2% of Avonex-treated patients.

In controlled trials, serious events related to depression, suicidal ideation, or suicide attempt occurred in 0.5% of Zinbryta-treated patients, in 0.5% of Avonex-treated patients, and in no placebo-treated patients.

In controlled and uncontrolled studies, 8 of 1485 (0.5%) Zinbryta-treated women developed breast cancer, with a rate of 185/100,000 patient years for all women in the studies, and a rate of 212/100,000 patients years including only European women (all 8 patients who developed breast cancer were from outside of the United States). This compares to a SEER rate for females < 50 years old of 43/100,000 and a Globocan rate of 102 to 213/100,000 in the age range of 40 to 55 years old. The mean and median age for all subjects in the database was 36 years old and there were no subjects older than 56 years. The rate in the clinical trials database exceeds the rate expected based on the background rate. One case of breast cancer occurred in a male patient (1/751); the incidence in males in the database is 43/100,000 patient years compared to the SEER rate for males of all ages of 1/100,000.

- F. Under section 505-1(a)(1)(F), FDA considers “[w]hether the drug is a new molecular entity.” The term “new molecular entity” generally is not applied to biologics, but we note that daclizumab was the subject of a previously approved BLA (Zenapax; BLA 103749).

The elements of the REMS for Zinbryta (daclizumab) will be a communication plan, elements to assure safe use, including that healthcare providers who prescribe Zinbryta must be specially certified, that pharmacies that dispense Zinbryta must be specially certified, that Zinbryta must be dispensed to patients with evidence or other documentation of safe-use conditions, that each patient using Zinbryta is subject to certain monitoring, and that each patient using Zinbryta is enrolled in a registry, an implementation system, and a timetable for the submission of assessments of the REMS.

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/s/

ALICE HUGHES
05/26/2016