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RESEARCH**

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

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Application Type	BLA
Application Number	761053
PDUFA Goal Date	12/28/2016
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Review Completion Date	09/26/2016
Subject	Evaluate of the need for a REMS
Established Name	Ocrelizumab
(Proposed) Trade Name	Ocrevus
Applicant	Genentech, Inc.
Therapeutic Class	Cytotoxic-Reductive Agent
Formulation(s)	Solution for Injection
Dosing Regimen	Initial Dose: 600 mg dose is administered as two separate intravenous (IV) infusions; first as a 300 mg infusion followed 2 weeks later by a second 300 mg infusion. Subsequent doses: 600 mg dose is administered as a single IV infusion every 6 months.

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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 the new molecular entity (NME) ocrelizumab is necessary to ensure the benefits of this product outweigh its risks. Genentech, Inc. submitted a Biologic Licensing Application (BLA-761053) for ocrelizumab with the proposed indication for treatment of patients with primary progressive multiple sclerosis (PPMS) and relapsing forms of multiple sclerosis (RMS). The Applicant did not submit a REMS with this application but did submit a Risk Management Plan (RMP) which proposes post-marketing safety studies to further assess long term safety data.

Healthcare providers who treat RMS and PPMS are typically specialists and are familiar with the risk of infusion related reactions and infection with similar therapies such as alemtuzumab and natalizumab and as well as the importance of patient monitoring. The serious risks associated with ocrelizumab are infusion related reactions, infection, and malignancy. Given the established relationship between other anti-CD20 monoclonal antibodies, such as rituximab, and infusion related reactions, including infusion related reactions as a warning with recommendations for pretreatment will be used to communicate and mitigate this risk. Ocrelizumab is associated with a risk of infections and uncertainty exists in whether outcomes of infections would be more serious in an unmonitored outpatient setting or in patients with greater risk for immunosuppression. Labeling infections as a warning would highlight the need for awareness of the potential for infections. Ocrelizumab is associated with an increased risk of malignancies, particularly breast cancer. Labeling malignancies as a warning would highlight the need for awareness of the potential. Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks of infusion related reactions, infections, and malignancy.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) ocrelizumab is necessary to ensure the benefits of this product outweigh its risks. Genentech, Inc. submitted a Biologic Licensing Application (BLA-761053) for ocrelizumab with the proposed indication for treatment of patients with primary progressive multiple sclerosis (PPMS) and relapsing forms of multiple sclerosis (RMS). This application is under review in the Division of Neurology Products (DNP). The Applicant did not submit a REMS with this application but proposed post-marketing safety studies to further assess the long-term safety data. The studies are intended to collect pregnancy-related safety data as well as to characterize the potential risk of malignancy and serious infections in patients with multiple sclerosis (MS) exposed to ocrelizumab as part of a risk management plan.

2 Background

2.1 Product Information

Ocrelizumab, a new molecular entity, is an anti-CD20 recombinant humanized monoclonal antibody proposed for treatment of patients with PPMS and RMS. CD20 is a cell surface antigen found on pre-B

cells, mature and memory B cells, but not expressed on lymphoid stem cells or plasma. Although the exact mechanism by which ocrelizumab exerts its clinical effect is not clear, it is thought to achieve immunomodulation by selectively depleting CD20 expressing B cells which is thought to be responsible for the consequent improvement in the diseases course of MS.¹

The proposed initial dose of ocrelizumab is 600 mg administered as two separate intravenous (IV) infusions, first as a 300 mg infusion followed 2 weeks later by a second 300 mg infusion. The subsequent doses are administered as 600 mg IV as a single infusion every 6 months. The product is proposed to be available as 300 mg/10 ml and must be further diluted before administration. Each initial infusion should be given over approximately 2.5 hours, and subsequent doses over approximately 3.5 hours. The Dosage and Administration section of the draft labeling submitted 04/28/2016 (and amended on 7/26/2016) recommends that patients should be pre-medicated with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each ocrelizumab infusion. Additional pre-medication with an antihistamine (e.g. diphenhydramine) is recommended approximately 30-60 minutes before each infusion of ocrelizumab. The addition of an antipyretic (e.g. acetaminophen) may also be considered.

Although approved for different indications, other anti-CD20 monoclonal antibodies include a boxed warning in their labeling. Rituxan (rituximab) which is indicated for Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), and Rheumatoid Arthritis (RA) has a boxed warning for fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, and Progressive Multifocal Leukoencephalopathy (PML). Gazyva (obinutuzumab) which is indicated for CLL in combination with chlorambucil has a boxed warning for hepatitis B and PML. Additionally, several medications approved for RMS including Gilenya (fingolimod), Tysabri (Natalizumab), Lemtrada (alemtuzumab), and Zinbryta (daclizumab) also have boxed warnings and REMS programs which are outlined in Table 1. The risks associated with these medications are not the same as those for ocrelizumab.

Ocrelizumab was granted fast track and priority designation for the treatment of patients with PPMS to delay the accumulation of physical disability as there is currently no available treatment approved for this indication.

Ocrelizumab is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for ocrelizumab, BLA 761053, relevant to this review:

- 04/04/2016: The Agency received Part 1 of the rolling submission for BLA 761053 for treatment of PPMS and RMS which included a letter of approval for fast track designation for PPMS.

¹ Kappos, L. et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomized, placebo-controlled, multicentre trial. *Lancet*. 2011, Nov 19; 379 (9085): 1779-87

- 04/28/2016: The Agency received Part 2 of the rolling submission for BLA 761053 for treatment of PPMS and RMS received which included proposed post-marketing safety studies intended to collect pregnancy-related safety data as well as to characterize the potential risk of malignancy and serious infections in patients with multiple sclerosis exposed to ocrelizumab.
- 06/24/2016: The Agency determined the review classification for this application is Priority
- 08/09/2016: A Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, a REMS was not needed for ocrelizumab, at this time.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition^{2,3,4}

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.⁵ 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, Minnesota⁶. The use of this rate and the U.S. Census Bureau estimated population⁷ 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.⁸

² Olek MJ and Mowry E, 2016, Pathogenesis and epidemiology of multiple sclerosis. In: UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA.

³ Olek MJ, 2016, Clinical course and classification of multiple sclerosis. In:UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA

⁴ Genentech, Inc. Ocrelizumab BLA 761053, received April 28, 2016, Section 2.5, Clinical Overview.

⁵ FDAAA factor(B): The seriousness of the disease or condition that is to be treated with the drug

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

⁷ United States Census Bureau Population Clock (accessible at <http://www.census.gov>)

⁸ FDAAA factor (A): The estimated size of the population likely to use the drug involved.

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 known as secondary progressive MS (SPMS) where there is a progressive worsening of neurologic function and accumulation of disability over time. Patients with SPMS may or may not continue to experience relapses due to inflammation as the disease gradually changes from an inflammatory process to a progressive phase characterized by nerve damage or loss.

PPMS is characterized by a progressive accrual of disability from the disease onset without discernible relapses and remissions leading to irreversible central nervous system damage. This type of MS is relatively rare and accounts for approximately 10-15% of all people with MS.⁹ Patients with PPMS are generally older at diagnosis with men and women affected equally. The pathophysiology of PPMS is poorly understood, but is thought to involve nerve degeneration with less inflammation than is seen in RMS¹⁰. Due to the progressive nature of the disease course, PPMS patients tend to have the poorest prognosis in terms of disability outcomes¹¹.

3.2 Description of Current Treatment Options¹²

A number of immunomodulatory agents, including various preparations of interferon beta, glatiramer acetate, natalizumab, alemtuzumab, daclizumab, dimethyl fumarate, teriflunomide, and fingolimod, are approved treatments for patients with RMS. These disease-modifying treatments reduce the relapse rate and improve brain MRI measures of MS disease activity. There is currently no approved disease modifying treatment option for PPMS.

Interferon beta therapies and glatiramer acetate require either intramuscular (IM) or subcutaneous (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

⁹ Lublin FD, et al. Defining the clinical course of multiple sclerosis; the 2013 revisions. *Neurology* 2014; 83:278-286

¹⁰ Miller HD, et al. Primary-progressive multiple sclerosis *Lancet Neurology* 2007; 6:903-12

¹¹ Rojas JI, et al. Interferon Beta for primary progressive multiple sclerosis. *Cochrane Database Syst Rev* 2010; 1:CD006643

¹² Olek MJ. 2016. Disease-modifying treatments of relapsing-remitting multiple sclerosis in adults. In:UpToDate, Gonzalez-Scarano F, Dashe JF (Eds), UpToDate, Waltham, MA

associated with the serious and potentially fatal risk of progressive multifocal leukoencephalopathy (PML). 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. Daclizumab is the most recently approved (May 2016) therapy for RMS and is available as a SC injection. Due to safety concerns including hepatic injury and other immune mediated disorders, daclizumab 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 RMS and includes the warnings and precautions, boxed warnings, 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)	Warnings/Precautions	Boxed Warning	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)	Severe hepatic injury, including rare cases of hepatic failure, has been reported. Monitor patients for signs of hepatic injury. [Avonex, Plegridy] Postmarketing reports of autoimmune disorders of multiple target organs included ITP, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis.	No Boxed Warning	No REMS
Copaxone (1996) (glatiramer acetate)	Postmarketing experience - liver function abnormalities, liver damage, hepatitis, cirrhosis	No Boxed Warning	No REMS
Tysabri (2004) (natalizumab)	Herpes encephalitis and meningitis, hepatotoxicity, hypersensitivity reactions, immunosuppression, infections	Progressive multifocal leukoencephalopathy	REMS necessary for the risk of Progressive multifocal leukoencephalopathy. REMS includes: Medication Guide Elements to Assure Safe Use

Drug (Date Approved)	Warnings/Precautions	Boxed Warning	Type of REMS Risk(s) the REMS is to mitigate
Gilenya (2010) (fingolimod)	Infection, progressive multifocal leukoencephalopathy, posterior reversible encephalopathy syndrome, respiratory effects, liver injury, fetal risk, increased blood pressure, basal cell carcinoma	No Boxed Warning	REMS necessary for the risk of Bradyarrhythmia and atrioventricular block, infections, macular edema, posterior reversible encephalopathy syndrome, respiratory effects, liver injury, and fetal risk. REMS includes: Communication Plan
Aubagio (2012) (teriflunomide)	Accelerated elimination if administered with cholestyramine or activated charcoal for 11 days. May decrease WBC, monitor for infection, hypersensitivity and skin reactions including Stevens-Johnson syndrome, peripheral neuropathy, increased blood pressure	Hepatotoxicity Risk of Teratogenicity	No REMS
Tecfidera (2013) (dimethyl fumarate)	Anaphylaxis and angioedema, progressive multifocal leukoencephalopathy, lymphopenia	No Boxed Warning	No REMS
Lemtrada (2014) (alemtuzumab)	Thyroid disorders, autoimmune cytopenias, active infections	Autoimmune conditions, infusion reactions, must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions, malignancies including thyroid cancer, melanoma, and lymphoproliferative disorders	REMS necessary for the risk of Autoimmune conditions, infusion reactions, malignancies. REMS Includes: Communication Plan Elements to Assure Safe Use
Zinbryta (2016) (daclizumab)	Hypersensitivity reactions, infections, depression and suicide	Severe liver injury including life threatening events, liver failure and autoimmune hepatitis. Contraindicated in patients with pre-existing liver disease or hepatic impairment.	REMS necessary for the risk of Hepatic injury including autoimmune hepatitis and other immune-mediated disorders REMS Includes: Communication Plan Elements to Assure Safe Use

4 Benefit Assessment

The efficacy of ocrelizumab for treatment of RMS is supported by two global pivotal Phase III studies, OPERA I and OPERA II (WA21092 and WA21093) in people 18-55 years of age with RRMS or SPMS with relapses (PPMS patients were excluded). Patients were included if they had 2 or more relapses in 2

years or one relapse in the year before screening and an expanded disability status scale (EDSS) score from 0-5.5 points. Both trials compared ocrelizumab 600 mg IV vs. interferon beta-1a 44 mcg SC in a multicenter, randomized, double-blind, double-dummy, parallel-group, comparator controlled study with treatment period of 96 weeks and optional open-label extension to ocrelizumab for eligible patients. The primary endpoint was annualized relapse rate (ARR) at 96 weeks. Secondary endpoints included confirmed disability progression (CDP) sustained for at least 12 weeks, CDP sustained for at least 24 weeks, confirmed disability improvement (CDI) at 12 weeks, Multiple Sclerosis Function Composite, Gadolinium-enhancing lesions as seen on MRI, T2 hyperintense lesions as seen on MRI, T1 hypointense lesions as seen on MRI, brain volume as seen on MRI, no evidence of disease activity (NEDA), and health-related quality of life as shown by SF-36 physical component survey (PCS).

The efficacy of ocrelizumab for treatment of PPMS is supported by a pivotal Phase III study, ORATORIO (WA25046) in people aged 18-55 with PPMS and EDSS at screening from 3.0-6.5 points. WA25046 was a multicenter, randomized, parallel-group, double-blind, placebo controlled study to evaluate the efficacy of ocrelizumab in adults with PPMS. The primary endpoint was time to onset of CDP sustained for at least 12 weeks. Secondary endpoints included time to onset of CDP sustained for at least 24 weeks, change in timed 25-foot walk, change in T2 lesion volume as seen on MRI, change in brain volume as seen on MRI, and quality of life as indicated on the SF-36 PCS.

Open-label extension (OLE) trials are ongoing for patients who completed the double-blind treatment period in each study.

A multicenter, randomized, parallel-group, partially blinded, placebo and interferon beta-1a controlled phase II dose finding study to evaluate the efficacy as measured by brain MRI lesions and safety of two dose regimens of ocrelizumab in patients with RRMS (WA21493) and OLE were included in the safety analysis. The OLE for this study is ongoing. Data from all MS patients who received any part of an ocrelizumab infusion at any dose was included to evaluate the long-term safety of ocrelizumab across MS. Additionally, safety data was included from nine RA studies to provide combined comparative safety data of ocrelizumab at different doses relative to a placebo control and to include longer term safety data of ocrelizumab treatment within the RA indication.

[REDACTED] (b) (4)

OPERA I and OPERA II Results

Patients enrolled in OPERA I (N=821) and OPERA II (N=835) were randomized 1:1 to interferon beta-1a or ocrelizumab. Ocrelizumab significantly reduced the protocol defined ARR in OPERA I and OPERA II by 46.4% and 46.8% (p<0.0001) at 96 weeks vs. interferon beta-1a, respectively. Results of secondary

endpoints supported the primary endpoint showing significantly greater reduction in measures of disability and MRI measures compared with interferon beta-1a.

Results for secondary endpoints of CDP for 12 weeks, CDP for 24 weeks, and CDI for 12 weeks were pooled from both studies due to insufficient statistical power to detect treatment differences between ocrelizumab and interferon beta-1a over the course of the study duration of 96 weeks. Ocrelizumab significantly reduced the 12-week CDP by 40% ($p=0.0006$) and reduced the 24 week CDP by 40% ($p = 0.0025$) vs interferon beta-1a. Treatment with ocrelizumab was associated with a 33% increase in the proportion of patients with 12-week CDI relative to interferon beta-1a ($p = 0.0194$). Ocrelizumab was shown to significantly reduce the relapse rate as well as improve disability scores and MRI results vs. interferon beta-1a showing efficacy for treatment of RMS.

ORATORIO Results

A total of 732 patients were enrolled in the study and were randomized 2:1 to ocrelizumab or placebo. 725 patients received treatment due to dropout. A 24% reduction in the risk of 12-week CDP was found in the ocrelizumab group vs. placebo (hazard ratio 0.76 [95% confidence ratio 0.59, 0.98], $p = 0.0321$). The secondary endpoints for disability (25% risk reduction of 24-week CDP [$p=0.035$]) and MRI outcomes (29% relative reduction in the progression rate in T25-FW, 3.4% decrease in T2 hyperintense lesion volume on ocrelizumab vs an increase of 7.4% on placebo, and 17.5% relative reduction in the rate of brain volume loss from week 24 to week 120) supported the primary endpoint to show statistically significant efficacy of ocrelizumab compared with placebo. The goal of therapy in the treatment of PPMS is to slow the progression and accumulation of disability. Ocrelizumab was shown to reduce the CDP vs. placebo in this patient population.

The clinical reviewer¹³ concluded that two adequate and well controlled trials provide substantial evidence that treatment with ocrelizumab reduces the frequency of relapses, the number of periods of disability progression lasting 12 and 24 weeks as measured by the EDSS scale, and evidence of disease activity on MRI scans in comparison to treatment with interferon beta-1a in patients with relapsing forms of MS. A single adequate and well controlled trial provides evidence that treatment with ocrelizumab reduces the occurrence of periods of disability in patients with PPMS. The pre-specified primary endpoint was met; however, the result is not robust and is sensitive to the methods of handling missing data. At the time of this review, the analysis of the efficacy of ocrelizumab in PPMS is ongoing.

¹³ Rodichok, L. DRAFT Clinical Review, Division of Neurology Products for ocrelizumab BLA 761053, dated 09/01/2016

5 Risk Assessment¹⁴

To perform a comprehensive assessment of the safety of ocrelizumab, data was pooled from the Phase III studies in patients with RMS and PPMS as well as a Phase II study in patients with relapsing remitting MS (RRMS) and nine other studies in patients with rheumatoid arthritis (RA).

The most frequently reported AEs were infusion related reactions (IRRs) and infections, which is expected from a B-cell depleting monoclonal antibody.

Eight deaths were reported in patients who received ocrelizumab in the MS program. Three were from the phase II study WA2193 in RRMS (systemic inflammatory response syndrome, injury, and unknown cause), one (<1%) was from the RMS trials (suicide), and four (<1%) were from the PPMS trial (pulmonary embolism, pneumonia, metastatic pancreatic carcinoma, and pneumonia aspiration). Two (<1%) deaths were reported in RMS patients in the interferon beta-1a group (suicide and mechanical ileus), and one (<1%) death was reported in the PPMS placebo arm (traffic accident).

Death was reported in 45 patients in the RA studies. The overall mortality rate for ocrelizumab patients in RA trials was 0.61/100 PY, 3.4-fold higher than the mortality in the MS trials. The clinical reviewer did not summarize 8 deaths given the remote likelihood of an association between ocrelizumab and the events. For the remaining 37 deaths, the reported causes of death were pneumonia (7), sepsis/septic shock (6), respiratory failure (3), lung cancer (3), sudden death/death (3), myocardial infarction (2), brain edema, breast cancer, carbon monoxide poisoning, disseminated intravascular coagulation, gastric cancer, gastrointestinal carcinoma, gastrointestinal hemorrhage, ischemic cerebral infarction, multi-organ failure, pulmonary embolism, ruptured cerebral aneurysm, toxicity to various agents, and traffic accident. The clinical reviewer notes that although the mortality rate for ocrelizumab and placebo were comparable in the controlled RA trials, the ocrelizumab groups had an increased number of infection/sepsis related deaths compared to placebo.¹⁵

5.1 Serious Adverse Events (SAEs)

In the RMS and the PPMS studies, the rate of SAE was similar between the ocrelizumab groups and the control groups: ocrelizumab (6.9%) vs. interferon beta-1a (8.7%) and ocrelizumab (20.4%) vs. placebo (22.2%), but was overall higher in the PPMS population. The most commonly reported SAE by system organ class was infections and infestations.

Although there was no imbalance in SAEs in overall psychiatric disorders in MS controlled trials, there was an imbalance in depression and suicide attempt SAEs that occurred only in ocrelizumab patients

¹⁴ Genentech. Summary of Clinical Safety, received 04/28/2016

¹⁵ Boehm, G. Clinical Safety Review, Division of Neurology Products/ODE1 for ocrelizumab BLA 761053 dated 09/14/2016

and not in comparator patients. Treatment emergent adverse events for depression occurred slightly more frequently in the RMS trials in ocrelizumab (8%) vs interferon (7%). Because interferon beta-1a labeling has a warning for depression and suicide, the clinical reviewer recommended considering a warning for depression and suicide for ocrelizumab.

5.2 Adverse Events of Special Interest (AESIs)

5.2.1 Infections

Serious infection was defined as any infection reported by the investigator as a “serious” adverse event or if a non-serious infection was treated with IV anti-infective treatment. This definition was used to allow direct comparison with data from RA trials where an imbalance of serious and opportunistic infections was seen.

The most common infections seen in the MS population were upper respiratory tract infection and urinary tract infection. The Applicant’s data showed that the infection rate was higher in patients with RMS treated with ocrelizumab (85.4 per 100 patient-years (PY)) vs. interferon beta-1a (69.1 per 100 PY); however, rates of serious infections were higher in the interferon beta-1a arm (2.43 per 100 PY) compared to ocrelizumab (1.24 per 100 PY). Infection rates in patients with PPMS were similar in both the ocrelizumab (76.5 per 100PY) and placebo groups (76.1 per 100PY). Serious infections in patients with PPMS were also similar in both ocrelizumab (3.74 per 100 PY) and placebo (4.24 per 100PY). There were no fatal infections in the RMS patients treated with ocrelizumab. Two fatal infections were noted in the PPMS trial in patients who received ocrelizumab (0.4%); pneumonia and pneumonia aspiration. The investigator determined that these events were not related to exposure to ocrelizumab; however, the Applicant assessed them as related given the infectious component in both cases. The clinical reviewer agreed that there was no obvious link between ocrelizumab in the case of aspiration pneumonia; the event was likely related to the patient’s dysphagia. However, for the pneumonia case, the clinical reviewer stated that ocrelizumab could have contributed to this event, but the exact diagnosis was unclear.

When viewed by severity grades, the clinical reviewer notes that the majority of infections in ocrelizumab patients were grade 1 or 2. In the controlled phases, compared to interferon or placebo, there were more ocrelizumab patients with grade 4 or 5 infections, but the number of such events was small and cannot support definitive conclusions regarding risk. In the controlled phases of MS trials, a higher percentage of comparator patients (interferon or placebo) experienced infection SAEs compared to ocrelizumab patients. The incidence of infections did not increase with subsequent dosing and there were no cases involving opportunistic infections, PML, or hepatitis B activation in any MS patients who received ocrelizumab.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] The rate of serious

infection was highest in patients who received ocrelizumab 1000 mg (7.28 per 100PY) compared with 400 mg (5.18 per 100PY) and placebo (3.99 per 100 PY). Differences between the RA and MS populations exist that could result in differences in infection rate when comparing them. The RA population is generally older with greater comorbid disease burden, and can be exposed to combination immunosuppressive therapy including glucocorticoids and use of disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and TNF- α inhibitors which could explain the imbalance.

5.2.3 Malignancies

An imbalance of malignancies was seen in both RMS and PPMS patients who were exposed to ocrelizumab vs. comparator where no imbalance in malignancy was seen in RA trials. During controlled phases on MS trials, 15 ocrelizumab patients (1.1%) had a malignancy diagnosis, 4 (0.5%) in the RMS trials and 11 (2.8%) in the PPMS trial, while 4 patients (0.4%) receiving comparator treatment had a malignancy diagnosis. Of specific types of cancers, the imbalance in breast cancers by treatment was most notable. There were 6 breast cancers in ocrelizumab patients, 2 from RMS trials and 4 from PPMS, and none in the comparator patients. When the data from all MS patients was pooled, breast cancer remained the most commonly reported malignancy with 8 out of 23 total malignancy cases being breast cancer (0.23/100PYs). The time from first ocrelizumab infusion to breast cancer ranged from 378-1298 days and the cumulative dose received ranged from 600-4600 mg. Basal cell carcinoma was the next most common being reported in 5 patients (0.1%) and occurring 5-87 months after the first dose of ocrelizumab.

The Applicant notes that the incidence rate in patients treated with ocrelizumab is consistent with epidemiological data as women with MS seem to have an increased risk of breast cancer, but that no conclusion can be made at this time concerning the risk of malignancy due to the low number of events and limited follow up.^{16,17} The Division of Neurology Products (DNP) consulted several other divisions including the Division of Oncology Products I (DOP-1), Division of Hematological Products (DHP), and Division of Epidemiology (DEPI) for further evaluation of the possible malignancy risk in MS patients exposed to ocrelizumab. The DEPI consultant reviewed the Applicant's comparisons of ocrelizumab clinical trial malignancy risk data to risk data from external sources which the Applicant felt was within the ranges reported in pooled placebo data from other MS clinical trials and published epidemiological data. The DEPI consultant concluded that these comparisons of clinical trial data with external data sources cannot be interpreted due to limitations including lack of control for potential confounding factors and lack of traditional analyses on the dose-response and time intervals between exposure and diagnosis.¹⁸ The consultants from DOP-1¹⁹ and DHP²⁰ reviewed the Applicant's presentations on

¹⁶ Nielsen NM, et al. Cancer risk among patients with multiple sclerosis: a population based register study. *Int J Cancer*. 2006. Feb 15; 118(4):979-84

¹⁷ Sun, ML, et al. Increased breast cancer risk for patients with multiple sclerosis: a nationwide population based cohort study. *European*

¹⁸ Braver, E. Safety Review Consult, Division of Epidemiology 1 for ocrelizumab BLA 761053, dated 07/18/2016

73% grade 1, 24% grade 2, 2.6% grade 3, and 0.1% (n=2) grade 4. Both of the grade 4 cases, one bronchospasm and one hypotension, occurred with the first dose of ocrelizumab in patients who received pretreatment with glucocorticoid but not antipyretic or antihistamine and resolved the same day. In the RMS trials, ocrelizumab patients pretreated with an oral antihistamine in addition to methylprednisolone had at least a 2-fold lower incidence in IRRs compared with pretreatment with methylprednisolone alone (with the exception of Dose 1, infusion 2). The label will include a warning about the risk of IRRs and recommend premedication with a steroid with optional antihistamine and antipyretic to reduce the risk and severity as well as include recommendations for managing IRRs. Additionally, the risks identified in the proposed labeling submitted on 04/28/2016 (and amended on 07/26/2016) include information regarding the risks of hypersensitivity reactions, infections, treatment with immunosuppressants before, during, or after ocrelizumab and the risks of administration of live vaccines listed in the Warnings and Precautions.

Malignancy, specifically a cluster of breast cancer, was identified as a potential safety signal needing further evaluation as no definite conclusion can be made from the available data. The Applicant has proposed long-term surveillance studies to address this. Due to the extended follow up period required to be able to detect an increase in malignancy risk and the indication of ocrelizumab to treat PPMS, a disease that has no other available approved therapy, performing this study pre-approval is not ideal. At the time of this review, labeling negotiations are ongoing. Additionally, DNP, DOP1, DHP, and DEPI agree that more information should be gathered to determine if there is a causal relationship between ocrelizumab and malignancy.

Alemtuzumab was approved for RMS with a REMS for malignancy. The clinical reviewer for alemtuzumab was able to show from the clinical trial data an increased risk for thyroid cancer and melanoma in patients treated with alemtuzumab and therefore it was determined that a REMS was necessary to ensure the benefits due to the risk of malignancy.²² With regard to ocrelizumab clinical trial data, causality cannot be attributed to ocrelizumab in any of the malignancy cases identified. The risk of malignancy can be communicated by adding information to the labeling in the Warnings and Precautions, the review division is still considering if a Boxed Warning is necessary to communicate this risk.

In addition, because interferon beta-1a labeling has a warning for depression and suicide and rates of depression were similar between ocrelizumab and beta-1a in clinical trials, the clinical reviewer recommended considering a warning for depression and suicide for ocrelizumab.

The overall safety profile of ocrelizumab appears to have comparable risk for serious adverse events compared to what is reported for other biologic treatments for RMS and for medications of the same class used for treatment of RA. Healthcare providers who treat RMS and PPMS are typically specialists and are familiar with the risk of IRR and infection with similar therapies and as well as the importance of patient monitoring. Based on the available data, if approved, risk mitigation measures beyond

²² Mentari, E. DNP/OND. Clinical Review Alemtuzumab, BLA 103948, dated 05/15/2014

professional labeling are not necessary for ocrelizumab for the treatment of RMS and PPMS. Therefore, DRISK and DNP have determined that a REMS is not warranted at this time to ensure that the benefits outweigh the risks of ocrelizumab.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS for ocrelizumab, but did propose risk management activities for ocrelizumab beyond routine pharmacovigilance and labeling described below.

8.1 Other Proposed Risk Management Activities

The Applicant proposed the following risk management activities:



DRISK defers to Division of Pharmacovigilance and Division of Pharmcoepidemiology for review and input.

9 Conclusion & Recommendations

Based on the available data, if approved, risk mitigation measures beyond professional labeling are not warranted for ocrelizumab for the proposed indication for treatment of patients with RMS and PPMS. PPMS is a highly debilitating condition for which no other treatment exists. Healthcare providers who treat RMS and PPMS are typically specialists and will be the likely prescribers of ocrelizumab. They are familiar with the risk of IRR and infection with similar therapies and as well as the importance of patient monitoring. Based on the risks associated with ocrelizumab in the clinical trials, a REMS is not necessary to ensure the benefits outweigh the risks. If new safety information becomes available, please consult DRISK.

10 Appendices

10.1 Materials Reviewed

1. Genentech. Original submission BLA 761053 for ocrelizumab, received 04/28/16
 - a. Section 1.16 Risk Management Plan
 - b. Section 2.5 Clinical Overview
 - c. Section 2.7.3 Summary of Clinical Efficacy
 - d. Section 2.7.4 Summary of Clinical Safety
2. Genentech. Proposed Prescribing Information for Ocrevus (ocrelizumab), received 04/28/2016, amended on 07/26/2016
3. Mid-cycle Meeting Background Package for ocrelizumab, dated 7/25/2016
4. Ison, G. Medical Officer Review of Consult, Division of Oncology Products-1 for ocrelizumab BLA 761053, dated 07/08/2016
5. Kanapuru, B. Medical Officer Review of Consult, Division of Hematology Products for ocrelizumab BLA 761053, dated 06/25/2016
6. Braver, E. Safety Review Consult, Division of Epidemiology 1 for ocrelizumab BLA 761053, dated 07/18/2016
7. Rodichok, L. DRAFT Clinical Review, Division of Neurology Products for ocrelizumab BLA 761053, dated 09/01/2016
8. Boehm, G. Clinical Safety Review, Division of Neurology Products/ODE1 for ocrelizumab BLA 761053 dated 09/14/2016

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/s/

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