CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	BLA
Application Number	761371
PDUFA Goal Date	September 13, 2024
Nexus TTT #	2023-7111
Reviewer Name(s)	May L Chan-Liston, PharmD, MPH
Team Leader	Jacqueline Sheppard, PharmD
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Review Completion Date	September 6, 2024
Subject	Evaluation of Need for a REMS
Proposed Nonproprietary Name	Ocrelizumab and hyaluronidase-ocsq
Proposed Proprietary Name	Ocrevus Zunovo
Name of Applicant	Genentech, Inc.
Therapeutic Class	CD20-directed cytolytic antibody
Formulation(s)	Solution for subcutaneous injection
Dosing Regimen	The recommended dosage of Ocrevus Zunovo is 920 mg/23,000 units (920 mg ocrelizumab and 23,000 units of hyaluronidase) administered as a single subcutaneous injection in the abdomen in every 6 months.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) is necessary to ensure the benefits outweigh its risks. Genentech, Inc. submitted a Biologic Licensing Application (BLA 761371) for Ocrevus Zunovo via the 351(a) regulatory pathway. The proposed indications are for the treatment of: 1.) Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults and 2.) Primary progressive MS, in adults. This application is under review in the Division of Neurology II (DN2). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) is a combination product of ocrelizumab and hyaluronidase for subcutaneous injection (ocrelizumab and hyaluronidase). Ocrelizumab is a recombinant humanized monoclonal antibody directed against CD20-expressing B-cells. Ocrevus (ocrelizumab) injection for intravenous use was approved in March 2017 and is indicated for 1.) Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults and 2.) Primary progressive MS, in adults.[1] Hyaluronidase (recombinant human recombinant) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Ocrevus Zunovo is proposed as a solution for subcutaneous injection (920 mg/23,000 units (920 mg ocrelizumab and 23,000 units of hyaluronidase) administered as a single subcutaneous injection in the abdomen over approximately 10 minutes every 6 months. The combination of ocrelizumab and hyaluronidase has not been marketed in any country.[2]

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761371 relevant to this review:

- 11/13/2023: Ocrelizumab and hyaluronidase submission for: 1.) Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults and, 2.) Primary progressive MS in adults was received.
- 04/22/2024: An internal mid-cycle meeting was held. Based on the available data at the time, it was determined that a REMS was not needed for the ocrelizumab and hyaluronidase-ocsq product.

2.3. Description of the Medical Condition

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. The cause of MS remains unknown. The most widely accepted theory is that MS begins as an inflammatory autoimmune disorder mediated by autoreactive lymphocytes. [3]

Relapsing forms of 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 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.[3]

Primary Progressive Multiple Sclerosis (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. PPMS is relatively rare and accounts for approximately 10–15% of all people with MS. 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 RMS. Due to the progressive nature of the disease course, PPMS patients tend to have the poorest prognosis in terms of disability outcomes.[3]

2.4. Description of Current Treatment Options

Treatment of relapsing forms of MS generally involves immunomodulation intended to reduce the frequency of clinical relapse. Many therapies approved for the treatment of relapsing forms of MS are labeled to prevent accumulation of disability. Treatment of PPMS involved immunomodulation to reduce clinical disease progression and the rate of disability progression.[4,5]

Over twenty products are used for treatment of RMS. 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.[4,5] Currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory mechanisms of action that impact the neuroinflammatory aspect of the disease.[4]

Ocrevus (Ocrelizumab) is the only approved treatment for PPMS. There is some evidence that ocrelizumab may reduce periods of disability lasting 12 and 24 weeks in patients with PPMS.[6]

3. Benefit Assessment

The Applicant submitted a BLA for ocrelizumab and hyaluronidase via the 351(a) pathway. The submission partially relied on the safety and efficacy data used for the approval of the intravenously-

administered ocrelizumab product. An ongoing Phase 3 Study, CN42097, was submitted for the efficacy and safety evaluation for ocrelizumab and hyaluronidase.[2]

CN42097 is a 96-week non-inferiority, randomized, open-label, parallel group, multicenter study trial designed to investigate the pharmacokinetics, pharmacodynamics, safety, and radiological and clinical effects of subcutaneous ocrelizumab and hyaluronidase versus intravenous ocrelizumab in subjects with relapsing forms of MS (RMS) or primary progressive MS (PPMS). Subjects were randomized 1:1 to receive treatment with either subcutaneous ocrelizumab and hyaluronidase 920 mg or ocrelizumab 600 mg (two 300 mg intravenous infusions administered 14 days apart) for 24 weeks. Subjects randomized to intravenous ocrelizumab then transitioned to subcutaneous ocrelizumab and hyaluronidase, for a total treatment duration of 72 weeks (last subcutaneous ocrelizumab and hyaluronidase injection at Week 48).[2]

The primary objective of Study CN42097 is to demonstrate the PK non-inferiority of subcutaneous ocrelizumab and hyaluronidase in subjects with RMS or PPMS based on the serum ocrelizumab area under the concentration-time curve from Week 1 to Week 12 (AUC_{W1-12}), compared to intravenous ocrelizumab. Secondary objectives were to examine the effects of subcutaneous ocrelizumab and hyaluronidase as compared to intravenous ocrelizumab on the following: maximum serum concentration (C_{max}), total number of T1 gadolinium- enhancing brain MRI lesions, total number of new or enlarging T2 brain MRI lesions, annualized relapse rate (ARR), expanded Disability Status Scale (EDSS), Treatment Administration Satisfaction Questionnaires (TASQ), subject satisfaction and preference of subcutaneous ocrelizumab and hyaluronidase over other previously received MS treatments, Patient Preference Questionnaire (PPQ), safety of subcutaneous ocrelizumab and hyaluronidase compared to intravenous ocrelizumab (as determined by adverse events (AEs), vital signs, and laboratory safety evaluations), evaluation of immune response, as determined by treatment-emergent anti-drug antibodies (ADAs), proportion of subjects with CD19+ B lymphocytes level of ≤5 cells/µL, serum neurofilament light (NfL) levels.[2]

There were 232 subjects in the PK-evaluable analysis set (n= 116 subcutaneous ocrelizumab and hyaluronidase, n=116 intravenous ocrelizumab) and 236 subjects in the safety-evaluable and efficacy-evaluable analysis sets (n=118 subcutaneous ocrelizumab and hyaluronidase, n= 118 intravenous ocrelizumab).[2]

The DN2 clinical reviewer concludes that the trial results established the PK non-inferiority of subcutaneous ocrelizumab and hyaluronidase compared to intravenous ocrelizumab based on the serum concentration of ocrelizumab. The secondary endpoint data also supports the conclusion, in which they demonstrated a similar total number of T1 gadolinium-enhancing and new or newly enlarging T2 MRI lesions in subjects treated with subcutaneous ocrelizumab and hyaluronidase compared to intravenous ocrelizumab.[6]

4. Risk Assessment & Safe-Use Conditions

The known risks associated with the intravenous form of ocrelizumab BLA 761053, is described in the approved Ocrevus labeling and include infusion reactions, infections (including serious infections),

progressive multifocal leukoencephalopathy, reduction in immunoglobulins, malignancies (including breast cancer), and immune-mediated colitis.[2,5]

The ongoing Phase III non-inferiority, randomized, open-label, parallel group, multicenter study (CN42097) and a Phase Ib, open-label, multicenter study (CN41144) to evaluate the PK, safety, tolerability, and immunogenicity of ocrelizumab and hyaluronidase administered by subcutaneous injection compared with 600 mg ocrelizumab administered as an intravenous infusion to subjects with MS.[2]

Key safety review issues identified by the DN2 clinical reviewer included injection-related reactions, hypersensitivity, headache, infections, reduction in immunoglobulins, cytopenia, malignancy, and immune-mediated colitis. Overall, the proportion of subjects who experienced SAEs was balanced between the groups however, Post Marketing Requirements (PMRs) will be issued for: 1.) injection-related reactions to obtain the adequate characterization of local and systemic injection-related reactions, 2.) (b) (4) (b) (4) and 3.) malignancies to determine the incidence and mortality rates of breast cancer and all malignancies in patients exposed to ocrelizumab.[6]

There were no deaths reported in Study CN42097. Two deaths occurred in Study CN41144. One death occurred during the Dose Escalation Phase in a subject previously treated with ocrelizumab who received ≥1 dose of subcutaneous ocrelizumab and hyaluronidase 1200 mg and experienced COVID-19 pneumonia. An additional death occurred during the Dose Escalation Phase in a subject previously treated with OCR who received one dose of intravenous ocrelizumab 600 mg and experienced cerebral infarction.[6]

The clinical reviewer concluded that the safety profile of subcutaneous ocrelizumab and hyaluronidase demonstrated to be consistent with that of intravenous ocrelizumab. Overall, the safety profile of both products appears comparable; however, this assessment is limited by the short duration of the Controlled Period (24 weeks) in study CN42097. The Applicant partially relied on supportive safety and efficacy evidence from BLA 761053 for Ocrevus; therefore, labeling for subcutaneous ocrelizumab and hyaluronidase will be aligned with that of Ocrevus.[6]

5. Expected Postmarket Use

Currently, a number of biologic treatments for MS are intravenously administered to patients in medical settings such as hospitals and infusion centers. Ocrevus is administered over 2 to 3.5 hours. The label for Ocrevus recommends that patients receive premedication (100 mg methylprednisolone and diphenhydramine) before each infusion to reduce the frequency and severity of infusion reactions and be monitored 1-hour post-infusion observation.[1]

Ocrevus Zunovo is expected to be administered via subcutaneous infusion by an HCP over a span of 10 minutes. The Ocrevus Zunovo label recommends oral premedication with 20 mg of dexamethasone (or an equivalent corticosteroid) and an antihistamine (e.g., desloratadine) administered at least 30 minutes prior to each Ocrevus Zunovo administration to reduce the risk of local and systemic injection reactions.

The addition of an antipyretic (e.g., acetaminophen) may also be considered.[7] Following initial treatment in the clinic or hospital, there is a potential ability of the administration of Ocrevus Zunovo to a patient by an HCP but provided at the patient's home. This may decrease the burden of patients who are in physical decline or have decreased mobility due to advancing MS. The administration of therapy would continue to be provided every 6 months and the patient should be monitored for 1 hour post injection,[6] the same as intravenous Ocrevus.[2]

6. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for ocrelizumab and hyaluronidase beyond routine pharmacovigilance and labeling.

7. Discussion of Need for a REMS

Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) for subcutaneous injection is proposed for the treatment of: 1.) Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults and 2.) Primary progressive MS, in adults. Currently, Ocrevus (ocrelizumab) for intravenous use is approved for the same indications for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.

The DN2 clinical reviewer recommends approval of Ocrevus Zunovo on the basis of the efficacy and safety information currently available.[6] Overall, the safety profile of both products appears comparable and risk mitigation measures beyond professional labeling and standard post marketing surveillance are not necessary to ensure the benefits of ocrelizumab and hyaluronidase-ocsq outweigh the risks.

8. Conclusion & Recommendations

Healthcare providers who treat RMS and PPMS are typically neurology specialists and are familiar with the risk of infusion related reactions and infection with ocrelizumab and other similar therapies. The HCPs are also aware of the importance of patient monitoring to manage the established risks. Based on the clinical review, the benefit-risk profile is favorable, and there are no clinical or safety differences between intravenous ocrelizumab and subcutaneous ocrelizumab and hyaluronidase-ocsq. Therefore, a REMS is not necessary for ocrelizumab and hyaluronidase-ocsq subcutaneous injection to ensure the benefits outweigh the risks. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be re-evaluated.

9. Appendices

9.1. References

[1] Genentech, Inc. Ocrevus (ocrelizumab) injection for intravenous use. Prescribing Information. 2017.

[2] Genentech, Inc. Ocrelizumab and hyaluronidase. Clinical Overview. November 13, 2023.

[3] Olek, MJ and Howard, J. Clinical presentation, course, and prognosis of multiple sclerosis in adults. In: UpToDate, Dashe, JF (Ed), Wolters Kluwer. (Accessed August 1, 2024).

[4] Olek, MJ and Howard, J. Treatment of acute exacerbations of multiple sclerosis in adults. In: UpToDate, Dashe, JF (Ed), Wolters Kluwer. (Accessed August 1, 2024).

[5] Zendel, L. Risk Assessment and Risk Mitigation Review of Ocrevus. Division of Risk Management. September 26, 2016.

[6] FDA. DRAFT Integrated Review for BLA 761371 Ocrelizumab and hyaluronidase-ocsq. Division of Neurology II. Accessed July 10, 2024.

[7] Genentech, Inc. Ocrevus Zunovo (ocrelizumab and hyaluronidase) injection for subcutaneous use. Draft Prescribing Information. September 6, 2024.

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