CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761142Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type	BLA
Application Number	761142
OSE RCM #	2019-1319
Reviewer(s)	Elizabeth Everhart, M.S.N., ACNP
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	5/14/2020
Subject	Evaluation of need for a REMS
Established Name	Inebilizumab
Trade Name	Uplizna™
Applicant:	Viela Bio
Formulation	Injection: 100 mg/10 mL (10 mg/mL) solution, single-use vial
Dosing Regimen	300 mg intravenous infusion followed 2 weeks later by a second 300 mg infusion, followed by a 300 mg infusion every 6 months thereafter
Indication	Treatment of neuromyelitis optica spectrum disorder (NMOSD)

Table of Contents

Executive Summary

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Uplizna™ (inebilizumab) is necessary to ensure the benefits of the drug outweigh the risks. Viela Bio submitted a Biologics License Application (BLA 761142) for inebilizumab on June 11, 2019. The proposed indication is for the treatment of neuromyelitis optica spectrum disorder. The most important safety concerns associated with inebilizumab are infusion reactions and serious infections, which include opportunistic infections such as hepatitis B virus reactivation, tuberculosis, and progressive multifocal leukoencephalopathy, as well as the risk for decreasing immunoglobulins over time, thereby potentially increasing the risk for infection. The Applicant included a Risk Management Plan in the submission that states a Risk Minimization Action Plan is not warranted and that use of the labeling and standard pharmacovigilance are adequate and sufficient for post-approval safety monitoring.

Neuromyelitis optica spectrum disorder is a rare, serious, inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage to the optic nerves and spinal cord, leading to severe visual loss and transverse myelitis. Inebilizumab showed substantial evidence of efficacy based on a significant reduction in the risk of adjudicated relapses compared to placebo. The Division of Risk Management has determined that a REMS is not needed to ensure the benefits of inebilizumab outweigh its risks. The prescribing population, mainly neurologists, should be familiar by their training and experience in the management of the adverse reactions associated with inebilizumab as monoclonal antibodies with similar safety profiles are approved for other serious neurological diseases that would be treated by the same prescribers, including eculizumab which is indicated for this disease state. Based on the safety profile and efficacy demonstrated in the clinical trial, the benefit-risk profile is acceptable and risk mitigation beyond the use of labeling is not required.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Uplizna™ (inebilizumab) is necessary to ensure the benefits of the drug outweigh its risks. Viela Bio (Viela) submitted a Biologics License Application (BLA 761142) for inebilizumab on June 11, 2019. The proposed indication is the treatment of neuromyelitis optica spectrum disorder (NMOSD). This application is under review in the Division of Neurology 2 (DN2). The Applicant did not submit a REMS but included a Risk Management Plan that states a Risk Minimization Action Plan is not warranted and that use of the labeling and standard pharmacovigilance are adequate and sufficient for post-approval safety monitoring.

2 Background

2.1 Product Information

Inebilizumab, a new molecular entity (NME)[a], is a humanized, immunoglobulin G1 monoclonal antibody that binds to the B-cell specific surface antigen CD19, resulting in depletion of B cells via antibody-dependent cellular cytotoxicity and cellular phagocytosis. Most patients with NMOSD have autoantibodies to a membrane protein named aquaporin-4 (AQP4) that is expressed on astrocytes and in other areas of the central nervous system (CNS). The AQP4 autoantibodies are implicated in the pathophysiology of NMOSD and are produced by a subpopulation of CD19-positive (CD19+) and CD20-negative (CD20-) B cells. Hence, inebilizumab's mechanism of action intends to deplete the population of B cells that are responsible for production of the autoantibody.

Inebilizumab is a chronic treatment to be supplied as a 100 mg/10 mL (10 mg/mL) solution in a single-use vial. The proposed dose is a 300 mg intravenous infusion, followed 2 weeks later by a second 300 mg infusion (to deplete newly recirculated B cells from the peripheral blood) followed by a single 300 mg infusion every 6 months thereafter.[b] Inebilizumab is not approved currently in any other jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for BLA 761142 relevant to this review:

- 2/10/2016: Orphan product designation granted for the treatment of NMOSD.
- 4/17/2019: Breakthrough therapy designation granted for NMOSD.
- 6/11/2019: BLA 761142 submission for the treatment of NMOSD.
- 11/18/2019: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that review of the safety database is ongoing and that several cases meeting international criteria for "possible" progressive multifocal leukoencephalopathy (PML) are under review.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

NMOSD is a rare, inflammatory disorder of the CNS characterized by severe, immune-mediated demyelination and axonal damage that mainly targets the optic nerves and spinal cord. In most patients, the pathophysiology of NMOSD is related to an autoimmune process mediated by a disease-specific antibody referred to as the aquaporin-4 (AQP4) autoantibody. AQP4 is a water channel membrane protein expressed predominantly on astrocytes. Binding of the autoantibody to the receptor initiates AQP4 down-regulation, complement activation, inflammation, and astrocyte injury.[1,2]

The clinical features of NMOSD include acute attacks of optic neuritis leading to severe visual loss, and transverse myelitis that often causes symmetric paraparesis or quadriparesis, sensory loss, and bladder dysfunction.[c] The disease typically follows a relapsing course. Attacks most often occur over days, with

---

[a] FDAAA factor (F): Whether the drug is a new molecular entity.
[b] FDAAA factor (D): The expected or actual duration of treatment with the drug.
[c] FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

variable degrees of recovery over weeks to months. Patients with NMOSD typically accumulate disability incrementally with each attack.[3] In some patients, optic neuritis and transverse myelitis occur concurrently, whereas in others, clinical findings are separated by a time delay. CNS involvement outside of the optic nerves and spinal cord can also occur and may include symptoms of intractable nausea, vomiting, hiccups, excessive daytime somnolence, reversible posterior leukoencephalopathy syndrome, neuroendocrine disorders, and (in children) seizures.[2]

The median age of disease onset is 32 to 41 years, but cases are described in children as well as older adults. A study in Olmsted County, Minnesota estimated the prevalence rate to be 3.9 per 100,000 persons and a prevalence of approximately 17,000 persons in the U.S. at the end of 2011. [d,4]

3.2 Description of Current Treatment Options

Eculizumab, a monoclonal antibody that inhibits complement activation, was approved in June 2019 for the prevention of recurrent attacks in patients who are AQP4 antibody-positive. Acute attacks and relapses of NMOSD are generally treated with intravenous glucocorticoids, such as high-dose methylprednisolone, followed by therapeutic plasma exchange for patients with refractory or progressive symptoms. Other unapproved but commonly used immunosuppressive agents for attack prevention include rituximab (which has a similar mechanism of action as inebilizumab, i.e., B cell depletion), azathioprine, and mycophenolate mofetil, though the evidence of efficacy of these agents comes mainly from observational studies and the clinical experience of experts. Azathioprine and mycophenolate typically require 4 to 6 months of use before onset of the biological effect and thus require bridging therapy with prednisone during this time. Observational evidence suggests multiple sclerosis disease-modifying therapies are ineffective or may even aggravate NMOSD, and therefore these therapies must be avoided.

The treatments currently in use are associated with various adverse effects, some serious. Eculizumab requires a REMS to mitigate the serious risks of meningococcal infections. Rituximab is associated with serious and potentially fatal infusion-related reactions, severe mucocutaneous reactions, hepatitis b virus reactivation, infections, and other serious reactions. Adverse effects of glucocorticoids include cataracts, hypertension, diabetes, and osteoporosis, among others. Azathioprine is associated with serious infections as well as hepatotoxicity, cytopenias, malignancies, and gastrointestinal toxicity. Serious adverse effects of mycophenolate include malignancies and infections, and embryofetal toxicity, for which a REMS is required; neutropenia can also occur.[5,6,7]

4 Benefit Assessment

The clinical study (CD-IA-MEDI-551-1155 (Study 1155) [NCT-02200770]) supporting the application is a phase 2/3 double-blind, placebo-controlled study in 231 patients with NMOSD who met certain criteria related to relapse history and disability scores. 213 patients were seropositive for autoantibodies against AQP4 and 17 patients were AQP4-seronegative. Patients were randomized 3:1 to receive inebilizumab

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

(n=175) 300 mg intravenous on Day 1 and on Day 15, versus placebo (n=56). Patients were followed for a period of 28 weeks, during which an adjudication committee evaluated possible NMOSD relapses. Patients completed the study when they experienced an on-trial relapse or if they completed the 28-week randomized controlled period without a relapse. Patients who completed the study were eligible to initiate inebilizumab (if they had been randomized to placebo) or continue treatment in an open label extension.

The primary efficacy endpoint in Study 1155 was the time to onset of the first adjudicated NMOSD attack as determined by the study Adjudication Committee (AC). Secondary endpoints included the worsening from baseline at the end of study using the Expanded Disability Status Scale[e] (EDSS); the change from baseline in low-contrast visual acuity binocular score; the cumulative total active MRI lesions during the study; and the number of NMOSD-related inpatient hospitalizations.

During the randomized controlled period, an adjudicated attack was observed in 21 (12%) of 175 patients in the inebilizumab group and in 22 (39%) of 56 patients in the placebo group. The hazard ratio (HR) of having an attack with inebilizumab treatment compared to placebo was 0.272 [95% CI 0.150 – 0.496] representing a 72.8% reduction in the risk of relapse ($p < 0.0001$). In the AQP4-seropositive population, an adjudicated attack was observed in 11% (18 of 161 patients) of the inebilizumab group compared with 42% (22 of 52 patients) of the placebo group (HR=0.227 [95% CI 0.121 – 0.423]).[f] Efficacy could not be interpreted in the AQP4-seronegative population due to the small number of patients and because no attacks occurred in patients who received placebo.

The Kaplan-Meier estimates for the time to first adjudicated attack in the total population is shown in Figure 1 below.

[e] The EDSS quantifies disability in 7 functional systems (pyramidal; cerebellar; brainstem; sensory; bowel and bladder; visual; and cerebral). The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death).

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

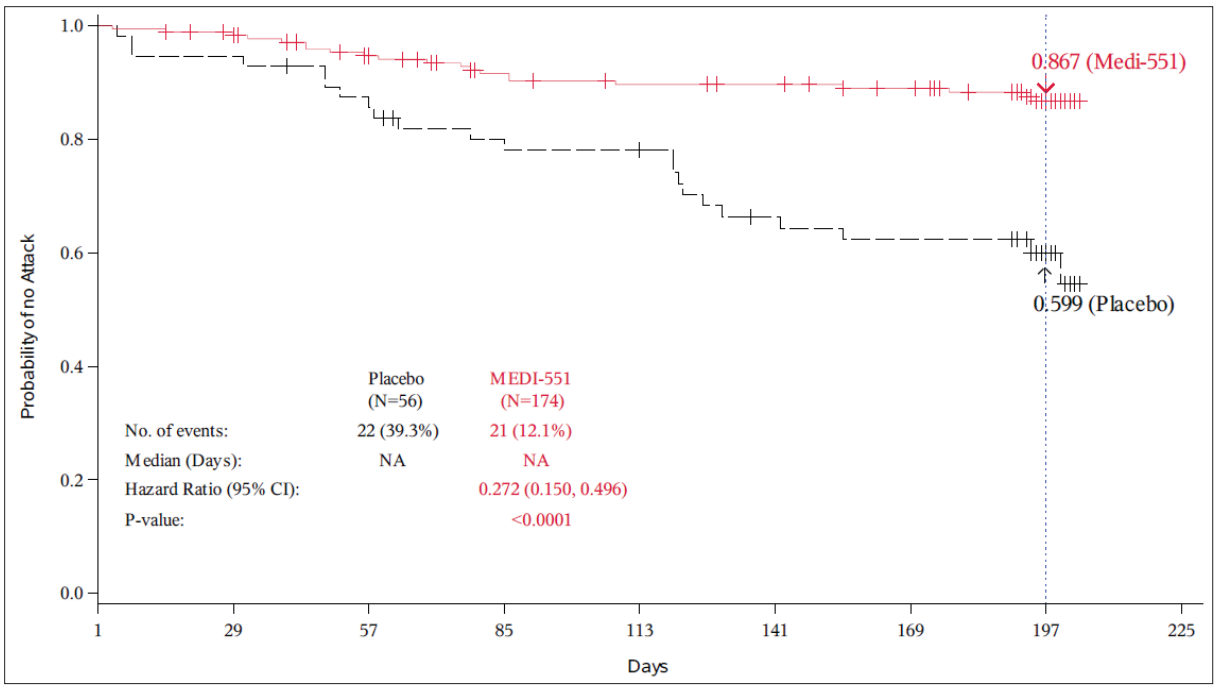

Figure 1. Kaplan-Meier survival estimates for time to first adjudicated attack

Medi-551 = inebilizumab
Source: Clinical Study Report CD-IA-MEDI-551-1155, Figure 14.2.5.1.1

In terms of the key secondary endpoints, worsening in the EDSS score from baseline to the end of study visit occurred at a lower rate in the inebilizumab group compared to the placebo group. However, the clinical reviewer noted the Applicant's analysis was flawed in that visits during an attack were included in the score calculation. The cumulative active number of MRI lesions and cumulative number of NMOSD-related inpatient hospitalizations were lower in the inebilizumab group compared with the placebo group. No difference was found between the inebilizumab and placebo groups in the change from baseline in low-contrast visual acuity binocular score.[8]

The clinical reviewer concluded that the time to the first AC-confirmed NMOSD relapse was significantly prolonged. This benefit was limited to the anti-AQP4 IgG seropositive patients, not to the broader indication of all NMOSD proposed by the sponsor.

5 Risk Assessment and Safe-Use Conditions

The NMOSD safety population is comprised of 225 patients with NMOSD who were treated with inebilizumab in Study 1155 and the open label extension. An additional 45 patients with systemic sclerosis or multiple sclerosis received inebilizumab in phase 1 clinical studies.[9]

5.1 SERIOUS ADVERSE EVENTS[g]

There were four deaths reported in the clinical development program, two of which occurred in patients being treated for NMOSD:

- A 31-year-old wheelchair-bound man with a long history of NMOSD was randomized to the placebo group and experienced an NMOSD attack of myelitis. He received IV corticosteroids as rescue therapy but did not improve. The patient entered the open label extension, received a dose of inebilizumab, and experienced sudden death 10 days later. The investigator felt that the death may have been due to NMOSD involvement of the high cervical spinal cord.
- A 67-year-old woman with NMOSD was randomized to the inebilizumab group. On study Day 177, she experienced an attack and was treated with IV corticosteroids. The patient entered the open label extension and received the third dose of inebilizumab. Nine days later, the patient was hospitalized for aphasia and right hemiparesis. Progressive multifocal leukoencephalopathy (PML) was considered in the differential diagnosis, but JCV DNA testing by two independent laboratories was inconclusive. A third CSF sample was sent to the National Institutes of Health (NIH) to perform an ultrasensitive JCV PCR analysis, and JCV DNA was undetected by this assay. MRI exam showed lesions more consistent with an acute demyelinating syndrome. The patient died due to hospital-acquired, ventilator-associated pneumonia approximately 3 weeks after admission. The investigator considered the event related to inebilizumab.

Reviewer comment: Although the NIH laboratory did not detect JCV, the clinical reviewer concluded the clinical events and MRI changes were typical of PML and considered the event as possible PML.[10]

- A 47-year-old woman in the systemic sclerosis clinical study received 70 mg of an inebilizumab infusion and died approximately three and a half months later after developing sclerodermal renal crisis, gastric antral vascular ectasia, and respiratory failure. The investigator assessed the events as not related to inebilizumab.
- A 44-year-old woman in the multiple sclerosis clinical study experienced a fatal mixed drug overdose. Postmortem blood sample results were positive for morphine, hydrocodone, oxycodone, and other CNS-active agents. The death was assessed as not related to inebilizumab by the investigator.

No additional deaths were reported in the 120-day safety update.[11]

A total of 8 patients (4.6%) experienced at least one serious adverse event (SAE) in the inebilizumab group compared with 5 patients (8.9%) in the placebo group. Two inebilizumab-treated patients experienced serious hepatobiliary adverse events (acute cholangitis, acute cholecystitis, hepatic function abnormal) compared with none in the placebo group. Serious infections (atypical pneumonia, urinary tract infection) were reported in two patients treated with inebilizumab and in two patients on placebo. During the open label extension, 21 patients (9.9%) had at least one SAE. Eleven of the 21 patients had serious infections, including 4 patients with urinary tract infections and 2 patients with pneumonia, one of which was a fatal event. There was one patient who developed a serious drug reaction with eosinophilia and systemic symptoms (DRESS) during the open label period.

---

[g] 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.

5.2 SEVERE ADVERSE EVENTS

Severe adverse events (AEs) were reported in 14 patients (8.0%) in the inebilizumab group compared with 7 patients (12.5%) in the placebo group. The most frequently reported severe AEs in the inebilizumab group were urinary tract infection and hypertension, which were experienced by 2 patients each. The severe AEs in the placebo group were each reported one time. In the open-label extension study, severe AEs were experienced by 23 patients (10.8%). The most frequently reported severe events were infections, which occurred in 10 patients, and severe musculoskeletal AEs, which occurred in 5 patients.

5.3 ADVERSE EVENTS OF SPECIAL INTEREST

Infusion-related reactions

Although infusion-related reactions occurred at a lower rate in the inebilizumab group compared with the placebo group, the sponsor noted that certain signs and symptoms (e.g., pruritus, vomiting) occurred at a higher rate in the placebo group that may reflect more disease activity in patients on placebo. There were no reports of anaphylactic reactions during the randomized controlled and open label periods. The proposed label includes a warning and precaution related to reducing the risk of and managing infusion reactions. If approved, labeling will include a contraindication for patients who have experienced life-threatening infusion related reactions to inebilizumab.

Infections[h]

Similar proportions of patients in both treatment groups had infections during the randomized controlled period (39% in the inebilizumab group and 44% in the placebo group). A smaller proportion of patients in the inebilizumab group (2.9%) had opportunistic infections compared to the placebo group (10.7%) during the randomized controlled period. During the open-label extension, 7.5% of patients who received inebilizumab developed opportunistic infections. Of the 21 inebilizumab-treated patients who experienced an infection during the controlled and open-label periods, the most frequently reported opportunistic infections were influenza (n=15) and herpes zoster (n=3).

If approved, labeling will include a warning and precaution for infections, with subsections described below for hepatitis B virus (HBV) reactivation, PML, tuberculosis, and vaccinations.

Hepatitis B reactivation

Labeling will note that the risk of HBV reactivation is increased because this product is a B-cell depleting antibody, although there were no cases of HBV reactivation in patients treated with inebilizumab. However, patients with chronic HBV infection were excluded from the clinical trials. The label will further advise that HBV screening be done in all patients before initiating treatment and the label will carry a contraindication for patients with active hepatitis infection.

Progressive Multifocal Leukoencephalopathy

[h] Patients with positive hepatitis B or C viral serology were excluded from Study 1155.

In addition to the fatal, possible PML case described above in Section 5.1, three other patients were evaluated for possible PML and were discussed in the clinical review.[12] In one patient, the clinical events did not suggest a specific diagnosis and the MRI results were not typical for PML; JCV testing was negative. The presence of anti-myelin oligodendrocyte glycoprotein antibodies in the case suggest the patient experienced an acute demyelinating event. The second patient developed new neurologic deficits and MRI lesions that are compatible with NMOSD; the patient experienced no clinical signs of PML and JCV testing was negative. The third patient developed MRI changes compatible with PML, but the clinical signs and symptoms were minimal and JCV testing was negative. If approved, the label will include a recommendation to withhold treatment and perform appropriate diagnostic evaluations at the first sign or symptom suggestive of PML.

Tuberculosis

The label will note that patients who had a history of a positive tuberculosis test were excluded from the clinical study unless they had been received appropriate treatment for tuberculosis; additionally, inebilizumab will be contraindicated in patients with active tuberculosis.

Vaccinations

The label will contain a recommendation within a subsection of the infections warning and precaution that all patients should be administered immunizations according to guidelines at least 4 weeks prior to beginning treatment with inebilizumab. A statement that the safety of immunization with live or live-attenuated vaccines following treatment was not studied and is not recommended during treatment and until a patient's B-cells are repleted. This subsection in labeling will also include a recommendation that infants of mothers who received inebilizumab during pregnancy should not receive live or live-attenuated vaccines unless there is confirmation that the infant's B-cells are repleted.

Reductions in Immunoglobulins

The clinical review[13] also notes a decrease in immunoglobulins and there is concern that over time, patients may be at increased risk for infection due to lower levels of immunoglobulins. The proposed label will include a warning and precaution describing the risk of a progressive decline in the level of immunoglobulins with a recommendation that levels of immunoglobulins be measured during treatment and until B-cell repletion.

6 Expected Postmarket Use

Inebilizumab is likely to be administered for the treatment of NMOSD in the outpatient setting in clinics, infusion centers, and physician offices. Home-based infusions are an additional option for patients who meet criteria set forth by payors, such as patients who have not previously experienced an infusion reaction to the drug. It is expected the prescribing community will largely be comprised of neurologists and may include other specialties such as internal medicine physicians. These prescribers should be familiar by their training and experience in the management of the adverse reactions associated with inebilizumab as monoclonal antibodies with similar safety profiles are approved for other serious neurological diseases that would be treated by the same prescribing population, including eculizumab which is also indicated for this disease state.

7 Risk Management Activities Proposed by the Applicant

The Applicant submitted a Risk Management Plan that stated a Risk Minimization Action Plan is not warranted and that use of the labeling and standard pharmacovigilance are adequate and sufficient for post-approval safety monitoring.

8 Discussion

The clinical reviewer concluded that substantial evidence of clinical efficacy has been established for the use of inebilizumab for the treatment of NMOSD in adult patients who are positive for anti-AQP4[14].

Neuromyelitis optica spectrum disorder is a rare, relapsing, inflammatory disorder of the CNS characterized by severe, immune-mediated demyelination and axonal damage that mainly targets the optic nerves and spinal cord. Most patients with NMOSD have autoantibodies to the AQP4 membrane protein expressed on astrocytes and in other areas of the CNS. The AQP4 autoantibodies are thought to be implicated in the pathophysiology of NMOSD and are produced by a subpopulation of CD19-positive (CD19+) and CD20-negative (CD20-) B cells. Inebilizumab's mechanism of action intends to deplete the population of B cells responsible for production of the autoantibody. The supporting phase 2/3 clinical trial found a significant effect on the time to first adjudicated on-trial relapse for inebilizumab compared with placebo. During the randomized controlled period of the trial, an adjudicated attack was observed in 11% (18 of 161 patients) of the inebilizumab group compared with 42% (22 of 52 patients) of the placebo group in the AQP4-seropositive population. The hazard ratio (HR) of having an attack on inebilizumab treatment compared to placebo was 0.227 [95% CI 0.121 – 0.423] representing a 77.3% reduction in the risk of relapse ($p < 0.0001$).

The most serious risks of inebilizumab include infusion-related reactions, which are an inherent risk with monoclonal antibodies, and infections. Although infusion-related reactions occurred at a lower rate in the inebilizumab group compared with the placebo group, Viela noted that certain signs and symptoms (e.g., pruritus, vomiting) occurred at a higher rate in the placebo group and may reflect more disease activity in patients on placebo. There were no reports of anaphylactic reactions during the randomized controlled and open label periods. The proposed label includes a warning and precaution related to reducing the risk of and managing infusion reactions. Similar proportions of patients in both treatment groups had infections (38% in the inebilizumab group and 41% in the placebo group). Serious infections were reported in 2 patients in the placebo group and 2 patients in the inebilizumab group. Opportunistic infections occurred in a greater proportion of patients in the placebo group (11%) than in the inebilizumab group (3%). Based on the drug's mechanism of action, infections are a risk associated with B-cell depleting therapy. It is unclear why the infection rate associated with inebilizumab, including that for opportunistic infections, was not higher than with placebo in the clinical trial. The clinical review[15] also notes a decrease in immunoglobulins and there is concern that over time, patients may be at increased risk for infection due to lower levels of immunoglobulins. The proposed label will include a warning and precaution for infections that includes a discussion of the risks of PML, reactivation of hepatitis B virus, and tuberculosis, as well as a warning and precaution for a reduction in immunoglobulins with a recommendation to monitor total and individual immunoglobulins while receiving inebilizumab. The clinical reviewer also recommends a PMR to monitor immunoglobulins.

Eculizumab, a monoclonal antibody that inhibits complement activation, was approved in June 2019 for the prevention of recurrent attacks in patients with NMOSD who are AQP4 antibody-positive. Eculizumab requires a REMS to mitigate the serious risks of meningococcal infections, which are related to the drug's effects on complement. Because inebilizumab has a different mechanism of action and does not inhibit complement, consideration for a REMS similar to that for eculizumab is not necessary.

Based on the observed benefit of inebilizumab and the seriousness of NMOSD, a chronic, rare disorder that can result in accumulating and severe disability, the risks associated with inebilizumab do not pose unique considerations for a REMS and can be communicated by the labeling. DRM is not recommending a REMS for the management of the risks of inebilizumab therapy.

9 Conclusion and Recommendations

Based on the currently available data, the benefit-risk profile of inebilizumab is favorable, therefore, DRM has concluded that a REMS is not necessary to ensure the benefits of inebilizumab outweigh the risks.

At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

[1] Weinshenker BG and Wingerchuk DM. Neuromyelitis Spectrum Disorders. Mayo Clin Proc 2017; 92:663-679.

[2] Hinson SR, et al. Molecular outcomes of neuromyelitis optica (NMO)-IgG binding to aquaporin-4 in astrocytes. PNAS 2012; 109:1245-1250.

[3] Rodichok L. Division of Neurology Products. Breakthrough Therapy Designation Determination Review, IND 117295, April 18, 2019.

[4] Flanagan EP, et al. Epidemiology of Aquaporin-4 Autoimmunity and Neuromyelitis Optica Spectrum. Ann Neurol 2016; 79:775–783.

[5] Azathioprine, Prescribing Information, accessed online at https://dailymed.nlm.nih.gov/dailymed/ March 25, 2019.

[6] Rituximab, Prescribing Information, accessed online at https://dailymed.nlm.nih.gov/dailymed/ March 25, 2019.

[7] Mycophenolate mofetil, Prescribing Information, accessed online at https://dailymed.nlm.nih.gov/dailymed/ March 25, 2019.

[8] Viela. Summary of Clinical Efficacy for inebilizumab, BLA 761142, June 11, 2019.

[9] Viela. Summary of Clinical Safety for inebilizumab, BLA 761142, June 11, 2019.

[10] Rodichok L. Division of Neurology Products 2. Draft Clinical Review, BLA 761142, January 15, 2020.

[11] Viela. 120-Day Safety Update, BLA 761142, October 10, 2019.

[12] See endnote 10.

[13] See endnote 13.

[14] Rodichok L. Division of Neurology Products 2. Draft Clinical Review, BLA 761142, February 21, 2020.

[15] See endnote 13.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELIZABETH E EVERHART
05/15/2020 08:13:12 AM

DONELLA A FITZGERALD
05/15/2020 09:11:27 AM

JAMIE C WILKINS PARKER
05/15/2020 10:40:06 AM