CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216834Orig1s000

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	NDA
Application Number	216834
PDUFA Goal Date	December 1, 2023
Nexus TTT#	2022-1164
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Review Completion Date	October 12, 2023
Subject	Evaluation of Need for a REMS
Established Name	Zilucoplan
Trade Name	Zilbrysq
Name of Applicant	UCB, Inc.
Therapeutic Class	Complement C5 inhibitor
Formulation(s)	Subcutaneous injection solution 40 mg/mL (single-use prefilled syringe)
Dosing Regimen	Dosed based on weight subcutaneously once daily

Body Weight	Once Daily Dosage
Less than 56 kg	16.6 mg
56 kg to less than 77 kg	23 mg
77 kg and above	32.4 mg

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zilbrysq (zilucoplan) is necessary to ensure the benefits outweigh its risks. UCB, Inc. submitted a New Drug Application (NDA) 216834 for zilucoplan with the proposed indication for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor antibody positive. The risks associated with zilucoplan include serious meningococcal infections, other infections caused by encapsulated bacteria, pancreatitis, and other pancreatic conditions. The Applicant's proposed Zilbrysq REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of zilucoplan outweigh the risk of serious meningococcal infections.

The benefits of treatment of gMG with zilucoplan were demonstrated in a phase 3, multicenter, randomized, double-blind, placebo-controlled study. In the zilucoplan treatment group, there were statistically significant decreases in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score and Quantitative Myasthenia Gravis (QMG) total score at Week 12 when compared with placebo. Although there have been no reported cases to date of serious meningococcal infections in the clinical development program for zilucoplan, there were risk mitigation measures (e.g., vaccination) in place to prevent infections. The risk of serious meningococcal infections is a known risk for the complement C5 inhibitors and other approved products (e.g., Soliris and Ultomiris) are subject to a REMS to mitigate this risk. The proposed label includes a boxed warning, a REMS, and warnings and precautions to mitigate the risk of serious meningococcal infections.

DRM and DN1 agree that a REMS is necessary to ensure the benefits of zilucoplan outweigh the risk of serious meningococcal infections. A REMS is necessary to ensure all prescribers are trained about the need to complete or update meningococcal vaccination at least 2 weeks prior to initiating zilucoplan, the need to provide antibacterial drug prophylaxis if urgent zilucoplan therapy is needed in patients that are not up to date on vaccinations, that patients and prescribers are aware of the life-threatening and fatal nature of meningococcal infections, and that prescribers and patients are aware of the signs and symptoms of meningococcal infection to monitor. The other risks (infections caused by encapsulated bacteria and pancreatitis) will be addressed through labeling in warnings and precautions. DN1 recommends approval of zilucoplan, with a REMS, for the treatment of gMG in adult patients who are anti-acetylcholine receptor antibody positive.

The goal of the Zilbrysq REMS is to mitigate the risk of serious meningococcal infections.

1) Patients are vaccinated against meningococcal infections caused by Neisseria meningitidis serogroups A, C, W, Y (MenACWY) and serogroup B (MenB) prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed.
2) Patients are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.
3) Prescribers are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

The Zilbrysq REMS includes the following REMS elements: ETASU A (healthcare providers who prescribe zilucoplan are specially certified), ETASU B (pharmacies that dispense zilucoplan are specially certified), ETASU D (dispensing of zilucoplan may be done only with the documentation of safe-use conditions), an implementation system, and a timetable for submission of assessments. Prescriber certification ensures that prescribers are knowledgeable about the risk of meningococcal infection associated with complement C5 inhibitors, the need to provide the appropriate vaccines against meningococcal infections prior to zilucoplan initiation, and the need for antibacterial drug prophylaxis if zilucoplan is initiated prior to the patient being up to date on meningococcal vaccines. As part of prescriber certification, they must certify, attest to comply with the requirements of the REMS, and counsel patients about the risk of meningococcal infections, the need for vaccination and antibacterial drug prophylaxis if needed, the signs and symptoms of meningococcal infection, and the need to seek immediate medical evaluation if these symptoms occur. Pharmacies must certify to ensure awareness of the risks and attest to complying with the requirements of the REMS by establishing processes and procedures to: 1) verify that prescribers are certified and 2) assess and document the patients' vaccination status including antibacterial drug prophylaxis prior to dispensing zilucoplan.

Based on the severity of the risk of serious meningococcal infections, DRM and DN1 agree that requiring a REMS consisting of prescriber certification, pharmacy certification, and documentation of safe use conditions (pharmacy assessment and documentation of meningococcal vaccination and antibacterial drug prophylaxis prior to dispensing) is necessary to ensure that the benefits outweigh the risks of zilucoplan. The REMS will also include an implementation system and timetable for submission of assessments.

1. Introduction

This review by the Division of Risk Management (DRM) and the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zilbrysq (zilucoplan) is necessary to ensure the benefits outweigh its risks. UCB, Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 216834 for zilucoplan with the proposed indication for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor antibody positive.[1] This application is under review in the Division of Neurology 1 (DN1). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of zilucoplan outweigh the risk of serious meningococcal infections.

2. Background

2.1. Product Information

Zilbrysq (zilucoplan), a new molecular entity[a], is a complement protein 5 (C5) inhibitor. Through the inhibition of C5, zilucoplan prevents downstream activation of the classical complement pathway which has been inappropriately activated in gMG patients. Zilucoplan inhibits the effects of C5 through two mechanisms: 1) binds to C5 to prevent its cleavage to C5a and C5b, and 2) binds to C5b to prevent binding to C6, and thus prevents assembly and activity of the membrane attack complex (MAC). Zilucoplan is proposed for the treatment of gMG in adult patients who are anti-acetylcholine receptor antibody positive.[2]

Zilucoplan is proposed for chronic use[b] and will be supplied as a 40 mg/mL subcutaneous injection solution single-use in prefilled syringes. The proposed dosing of zilucoplan is weight-based (16.6 mg, 23 mg, or 32.4 mg) administered via subcutaneous injection once daily. Zilucoplan is likely to be self-administered in the outpatient setting. Zilucoplan is not currently approved in any jurisdiction.

There are three complement inhibitors approved that are subject to a REMS: Soliris (eculizumab), Ultomiris (ravulizumab), and Empaveli (pegcetacoplan). Soliris and Ultomiris are complement C5 inhibitors that have a REMS to mitigate the occurrence and morbidity associated with meningococcal infections which include prescriber certification (ETASU A).[3,4] The approved Soliris REMS and Ultomiris REMS include ETASU A; (b) (4) [redacted].[5] Empaveli is a complement protein 3 (C3) inhibitor that is subject to a REMS to mitigate the occurrence and morbidity associated with encapsulated bacteria infections (*Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y, and B, and *Haemophilus influenzae*) which includes prescriber certification (ETASU A), pharmacy certification (ETASU B), and evidence of safe use conditions (ETASU D).[6]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216834 relevant to this review:

- **06/26/2019**: Orphan Drug Designation granted for treatment of gMG.
- **08/31/2022**: NDA 216834 submission for the treatment of gMG in adult patients who are anti-acetylcholine receptor antibody positive received.[1]
- **11/02/2022**: The Agency sent an information request to the Applicant requesting revision of the format of the REMS Document and Microsoft Word versions of all materials.[7]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- **11/14/2022**: Applicant submitted a REMS amendment including requested format changes to the REMS materials and REMS document.[8]
- **11/18/2022**: The Agency sent an information request to the Applicant with questions regarding the proposed REMS in reference to the vaccination reminder letters for prescribers, wholesaler-distributor requirements, and the REMS coordinating center.[9]
- **11/29/2022**: Applicant responded to the 11/18/23 to the information request explaining how the vaccination reminder letters will be generated and distributed, the distribution plan for zilucoplan, and the roles and responsibilities of the REMS coordinating center.[10]
- **02/16/2023**: A Mid-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant a REMS for zilucoplan (NDA 216834) is necessary to ensure that the benefits of the drug outweigh the risks of meningococcal infections, a review of the proposed REMS is ongoing, and further information will be communicated at a later date.[11]
- **04/05/2023:** The Agency sent an information request to the Applicant with questions regarding the authorization process for pharmacies to verify prescriber enrollment in the REMS prior to prescription dispensing.[12]
- **04/13/2023:** Applicant responded to the 4/05/23 information request regarding the pharmacy authorization process. The Applicant explained that the authorized representative will log in to the REMS web portal to verify prescriber certification using a look-up tool and a unique authorization code would not be generated for each dispense.[13]
- **06/02/2023:** Interim Comments were issued to the Applicant. Agency recommended revision of the REMS goal and objectives, revisions of the REMS Document to align with the REMS Document Technical Conformance Guide, addition of a section in the REMS Document for wholesaler, distributors, and other entities that distribute zilucoplan, and updates to the timetable for submission of assessments.[14]
- **06/16/2023:** Applicant submitted a REMS amendment in response to the Agency's June 2, 2023 comments.[15]
- **07/24/2023:** The Agency sent an information request to the Applicant with questions regarding pharmacy processes and key risk messages, and requesting submission of REMS materials impacted by an administrative change related to adverse event reporting.[16]
- **07/28/2023**: Interim comments were issued to the Applicant by the Division of Mitigation Assessment and Medication Error Surveillance and DRM. DRM contributed comments to the review related to revision of the REMS key performance indicator (KPI) and asked the Applicant to propose a KPI target threshold with supporting rationale.[17]
- **07/31/2023:** Applicant submitted a REMS amendment and response to the Agency's July 24, 2023 information request.[18]
- **08/04/2023**: Applicant submitted a communication in response to the comments sent on 07/28/2023 regarding the KPI.[19]

- **08/24/2023**: A draft label was sent to the Applicant that included the Agency's revisions to language pertaining to meningococcal vaccination and antibacterial drug prophylaxis.[20]
- **08/24/2023**: Interim comments issued to the Applicant. Agency recommended revision of the REMS goal and objectives, revisions to the REMS Document and materials to align with Agency labeling revisions, and updates to the key performance indicators and associated thresholds.[21]
- **08/29/2023**: Applicant submitted draft label and REMS materials with proposed revisions.[22,23]
- **08/30/2023:** Major amendment acknowledgement letter sent to the Applicant based on the REMS amendment submitted on August 29, 2023; PDUFA goal date extended by 3 months.[24]
- **09/08/2023:** Interim comments issued to the Applicant. Agency recommended revisions to the REMS Document and materials to align with Agency labeling revisions and updates to the key risk messages.[25]
- **09/15/2023:** Applicant submitted a REMS amendment in response to the Agency's September 8, 2023 comments.[26]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Myasthenia gravis is a chronic autoimmune disease of neuromuscular transmission that manifests in two clinical forms, ocular and generalized.[27] The clinical hallmark of the disease is weakness in ocular, bulbar, limb, and respiratory muscles.[28] In ocular myasthenia, weakness is limited to the eyelids and extraocular muscles, whereas the weakness in generalized myasthenia commonly affects ocular muscles as well as a variable combination of bulbar, limb, and respiratory muscles.[28] Weakness results from an antibody-mediated, T cell-dependent immunologic attack directed at acetylcholine receptors and/or receptor-associated proteins in the postsynaptic membrane of the neuromuscular junction.[27,28] Most patients with the generalized form of the disease are seropositive for antibodies, with 80-90% having autoantibodies against the acetylcholine receptor (AChR).[27] The worldwide prevalence rate of myasthenia gravis is estimated to range from 15 to 179 per million persons.[29] Use of the upper limit of that range and the current estimated population of 334 million[30] in the United States (U.S.), results in an overall crude U.S. prevalence of myasthenia gravis estimate of approximately 60,000 persons.[c]

Clinical symptoms of myasthenia gravis may include ocular ptosis or diplopia; bulbar symptoms such as dysarthria, dysphagia, and fatigable chewing; weakness of facial, neck, and proximal limb muscles; and respiratory muscle weakness, which is the most serious symptom. Respiratory muscle

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

weakness may lead to respiratory insufficiency or respiratory failure and death, which is referred to as myasthenic crisis.[28,d]

Early in the disease course, the symptoms of weakness are transient in many patients, with hours to days free of symptoms. The symptoms may remit spontaneously for weeks or longer. The progression of myasthenia gravis usually peaks within a few years of disease onset.[28] Although data are limited, a population study in Denmark found that seropositive myasthenia gravis may be associated with increased mortality.[31,e]

3.2. Description of Current Treatment Options

The initial treatment for most patients with myasthenia gravis is an oral acetylcholinesterase inhibitor, such as pyridostigmine, which decreases the degradation of acetylcholine in the neuromuscular junction.[32] Acetylcholinesterase inhibitors provide marked symptomatic improvement in some patients but little or no improvement in others. Most patients eventually require immunotherapy during the course of their disease. The complement C5 inhibitors, eculizumab[33] and ravulizumab[34], and the neonatal Fc receptor blockers, efgartigimod[35] and rozanolixizumab[36] are FDA-approved treatment options for myasthenia gravis. See Table 1 for a summary of the FDA-approved therapies for the treatment of myasthenia gravis.

Immunosuppressive agents such as glucocorticoids, azathioprine, mycophenolate mofetil, and cyclosporine are used as chronic treatments to bring about and maintain remission or clinical improvement.[32] However, except for pyridostigmine, most treatments are not FDA approved for the treatment of myasthenia gravis and these treatments typically take weeks to months before onset of clinical effect. These treatments are also associated with various adverse effects. Adverse effects of glucocorticoids may include cataracts, hypertension, diabetes, and osteoporosis. Azathioprine is associated with a flu-like illness as well as hepatotoxicity, cytopenia, and malignancies. The most common adverse effects of mycophenolate are gastrointestinal; leukopenia can also occur. Hypertension and nephrotoxicity are the most common limiting adverse effects of cyclosporine.[32]

In situations where rapid onset of effect is needed, such as in severe or rapidly worsening generalized disease, the use of plasmapheresis or intravenous immune globulin may be indicated. However, the duration of benefit with these rapid-acting treatments typically lasts only three to six weeks and these treatments are not FDA approved for the treatment of myasthenia gravis.[32,37]

Despite available therapies for treatment of myasthenia gravis, there remains an unmet medical need for effective treatments as not all patients are able to tolerate or benefit from the available therapies.

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

Table 1: FDA-Approved Therapies for the Treatment of Myasthenia Gravis[33-36,38]

Drug (Approval Date)	Indication	Dosing and Administration	Important Safety and Tolerability Issues	Risk Management Approaches
Mestinon-pyridostigmine (1955)	Myasthenia gravis	360 mg-960 mg PO daily in divided doses	Cholinergic crisis with overdose, bradycardia, salivation, abdominal cramps, diarrhea	Labeling- warnings and precautions
Soliris-eculizumab (2017)	Treatment of adult patients with gMG who are anti-AChR antibody positive	900 mg IV once a week for 4 weeks, 1200 mg IV on week 5, then 1200 mg IV every 2 weeks thereafter	Meningococcal infection, other infections, infusion-related reactions	REMS- ETASU Labeling- boxed warning, warnings and precautions
Vyvgart-efgartigimod alfa-fcab (2021)	Treatment of gMG in adult patients who are anti-AChR antibody positive	Weight less than 120 kg: 10 mg/kg IV once weekly for 4 weeks Weight 120 kg or greater: 1200 mg IV once weekly for 4 weeks	Infections and hypersensitivity reactions	Labeling- warnings and precautions
Ultomiris-ravulizumab-cwvz (2022)	Treatment of adult patients with gMG who are anti-AChR antibody positive	Weight-based IV infusion loading dose (2400 mg - 3000 mg) followed 2 weeks later by weight-based maintenance dosing (3000 mg - 3600 mg) every 8 weeks	Meningococcal infections, other infections, infusion-related reactions	REMS- ETASU Labeling- boxed warning, warnings and precautions
Rystiggo-Rozanolixizumab-noli (2023)	Treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive	Weight-based subQ infusion once weekly for 6 weeks; administer subsequent cycles based on clinical evaluation	Infections, aseptic meningitis, hypersensitivity reactions	Labeling- warnings and precautions

4. Benefit Assessment

The efficacy of zilucoplan in gMG was evaluated in one pivotal phase 3 trial, MG0010 (hereafter referred to as RAISE, National Clinical Trial [NCT] NCT04115293).[39] RAISE was a multicenter, randomized, double-blind, placebo-controlled study which evaluated 174 adult subjects (zilucoplan group=86, placebo group=88) with anti-acetylcholine receptor positive gMG. Subjects were randomized 1:1 to receive zilucoplan administered as a weight-based dose subcutaneously daily or placebo over a 12-week treatment period.[39] Subjects were provided the drug in single-use prefilled syringes containing fixed doses of 16.6 mg, 23 mg, and 32.4 mg based upon the weight range bracket into which the study subject fell. Subjects remained on stable doses of standard of care therapy including corticosteroids and immunosuppressants throughout the treatment period.[39]

The study population in RAISE had a mean age of 53 years and a mean time since diagnosis of 9 years. Most subjects were female (57%) and White (74%). The mean baseline Myasthenia Gravis-Activities of Daily Living[e] (MG-ADL) total score was 10.6 and approximately 50% of subjects were refractory to treatment at baseline. Approximately 85% of patients were receiving cholinesterase inhibitors and 63% were receiving corticosteroids for gMG at baseline. The baseline demographics were well-balanced between study groups.[39]

The primary endpoint was change from baseline to Week 12 in the MG-ADL total score. A key secondary endpoint was change from baseline to Week 12 of the Quantitative Myasthenia Gravis (QMG)[f] total score. The zilucoplan group had statistically significantly greater decreases in MG-ADL total score and QMG total score at Week 12 compared with placebo as outlined in Table 2 below.[39]

[e] The Myasthenia Gravis-Activities of Daily Living is an 8-item survey of MG symptom severity which assesses the impact of MG on patient daily functioning. The survey is based on the patient's recall of symptoms during the prior week. Each item is scored on a 0 to 3-point scale (0=no symptoms, 3=severe symptoms). The total score is the sum of the 8 individual scores and ranges from 0 to 24 with higher scores indicating more severe symptoms.

[f] The Quantitative Myasthenia Gravis score a 13-item strength scoring system that assesses muscle weakness including ocular, bulbar, respiratory, and limb muscles. Each item is scored on a 0 to 3-point scale (0=no weakness, 3=severe weakness) and the total score is the sum of the 13 individual scores (range 0 to 39).

Table 2. MG-ADL Total Score and QMG Total Score Change from Baseline to Week 12[39]

	Zilucoplan (n=86)	Placebo (n=88)	Zilucoplan change in least squares mean vs placebo (95% CI)	p-value
MG-ADL Total Score: Least Squares Mean (95% CI)	**-4.29 (-5.38, -3.5)**	**-2.3 (-3.17, -1.43)**	**-2.09 (-3.24, -0.95)**	**<0.001**
QMG Total Score: Least Squares Mean (95% CI)	**-6.19 (-7.29, -5.08)**	**-3.25 (-4.32, -2.17)**	**-2.94 (-4.39, -1.49)**	**<0.001**

The clinical reviewer concluded that the Applicant provided evidence of effectiveness based on the results of the RAISE study.[40,g]

5. Risk Assessment & Safe-Use Conditions

The primary safety population for zilucoplan consists of all subjects in the randomized population who received zilucoplan in the pivotal phase 3 trial, RAISE. The open-label, long-term extension safety data from the Phase 2 study, Study MG0009 (NCT03315130), and the Phase 3 study, Study MG0011 (NCT04225871) provide additional supportive safety data.[41]

The primary safety population includes 86 subjects randomized to zilucoplan dosed based on weight vs 88 subjects randomized to placebo.[42] The majority of subjects completed the 12 week duration of the study (95.5% of placebo group and 95.3% of zilucoplan group).[42] The most common adverse reactions (occurring in ≥ 5% of subjects treated with zilucoplan and more frequently than with placebo) were injection site reaction, upper respiratory tract infection, diarrhea, increased lipase, and increased amylase.[41]

Two additional study pools including study participants with gMG and immune-mediated necrotizing myopathy (IMNM) are used to summarize clinical safety and are described below.[41]

- Pool S1B: Long-Term Safety Pool (gMG only)
    - This cohort includes subjects with gMG who received zilucoplan either during the placebo-controlled studies or in the open-label extension studies. This pool includes Study MG0009 (both placebo-controlled portion and open-label extension), RAISE, and Study MG0011

[g] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

    - There were 212 subjects who received zilucoplan of approximately 0.3 mg/kg daily based on weight bracket either during the placebo-controlled studies or in the open-label extension studies
- Pool S2B: Long-Term Safety Pool (gMG and IMNM)
    - This cohort includes subjects with gMG and IMNM who received zilucoplan either during the placebo-controlled studies or in the open-label extension studies. This pool includes Study MG0009 (both placebo-controlled portion and open-label extension), RAISE, MG0011, and IMNM01 (both placebo-controlled and open-label extension)
    - There were 238 subjects who received zilucoplan of any dose either during the placebo-controlled studies or in the open-label extension studies

5.1. Deaths

A total of 10 deaths were reported in zilucoplan-treated subjects (Pool S2B), 1 death which occurred in the pivotal study, RAISE, and 9 deaths which occurred in the open-label extension studies (3 in MG0009, 5 in MG0011, and 1 in IMNM01).[41] Five of these deaths were reported as cardiac arrest or unknown cause. The 5 other deaths were due to an accidental head injury, COVID-19 (3 subjects), and pancreatic carcinoma. None of the deaths were considered treatment-related by the Applicant, however the clinical reviewer concluded that the possibility of zilucoplan accelerating the process in pancreatic cancer cannot be excluded.[40,41] See Section 5.3.2 for further discussion on pancreatic events.

5.2. Serious Adverse Events

In the pivotal study, RAISE, serious adverse events (SAEs)[h] occurred with similar incidence in the zilucoplan treated group compared with the placebo group (12.8% with zilucoplan and 14.8% with placebo).[41] The serious adverse events occurred with low frequency across many different system organ class categories with the most common serious adverse event being myasthenia gravis.

In the long-term safety pool in gMG subjects (Pool S1B), SAEs occurred in 29.1% of subjects treated with zilucoplan. In study MG0009 during the open label extension period, there were 44 total SAE's which included 5 pancreatic SAEs. In Study MG0011 there were 118 SAEs including 6 pancreatic SAE's. See Section 5.3.2 below for further discussion of pancreatic SAEs.[i]

[h] 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.

[i] Section 505-1 (a) of the FD&C Act: *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.*

5.3. Adverse Events of Special Interest

5.3.1. Serious Meningococcal Infections

Complement C5 inhibitors like zilucoplan can increase the risk of infections caused by serious encapsulated organisms, most notably *Neisseria meningitidis* infections. The complement C5 inhibitor Soliris (eculizumab) has been associated with a 1,000 to 2,000 fold increased risk for meningococcal infections when compared to the general population in the United States due to terminal complement inhibition.[43] Serious meningococcal infections are bacterial infections that present as meningitis, bacteremia, or both and can become rapidly life-threatening and fatal if not treated immediately.[44] Life-threatening and fatal meningococcal infections have occurred in patients receiving Soliris and Ultomiris.[33,34]

To date, there have been no reported cases of serious meningococcal infections in the clinical development program for zilucoplan.[41] In the RAISE clinical trial protocol, all study subjects were required to be vaccinated against meningococcal infections (with MenACWY and, where available in in accordance with local standard of care, MenB) within 3 years prior to, or at the time of initiating study treatment. Study subjects who initiated study treatment less than 2 weeks after receiving a meningococcal vaccine were treated with prophylactic antibiotics until at least 2 weeks after the initial vaccine dose.[42]

The Advisory Committee on Immunization Practices (ACIP) recommends vaccinating persons receiving a complement inhibitor with meningococcal vaccines for serogroups A, C, W, and Y (MenACWY vaccine) and serogroup B (MenB) due to the substantially increased risk for meningococcal infections in these patients.[44] Vaccinated patients receiving a complement C5 inhibitor may be still at risk for meningococcal infections, as the vaccines may not completely protect patients against meningococcal disease due to the C5 inhibition despite development of antibodies with the vaccines and due to non-groupable strains of *N. meningitidis* which the vaccines do not target.[45]

During the course of the review, DN1, the Division of Neurology 2 (DN2), the Division of Nonmalignant Hematology (DNH), and DRM met to discuss labeling of the complement C5 inhibitor class to clarify language in the label related to the need for meningococcal vaccines prior to starting complement C5 inhibitor therapy and optimal use of antibacterial drug prophylaxis. For further expertise on these topics, the Division of Anti-Infectives (DAI) and the Center for Biologics Evaluation and Research (CBER) were consulted regarding the labeling language.[46,47]

Given the complement C5 inhibitors are associated with an increased susceptibility to serious meningococcal infections, the review team recommends the risk of serious meningococcal infections be communicated in labeling in a boxed warning, a REMS, and language in Section 5: Warnings and Precautions.[40] The boxed warning states to complete or update meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to

administering the first dose of zilucoplan, unless the risk of delaying therapy outweighs the risk of developing a meningococcal infection, and to comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccinations in patients receiving a complement inhibitor.[2] Section 5, Warnings and Precautions, of the label further states to revaccinate patients in accordance with ACIP recommendations considering the duration of zilucoplan therapy. If urgent zilucoplan therapy is indicated in a patient who is not up to date with both MenACWY and MenB vaccines according to ACIP recommendations, administer meningococcal vaccines as soon as possible and provide the patient with antibacterial drug prophylaxis.[2] Patients should be closely monitored for early signs and symptoms of meningococcal infections and evaluated immediately if infection is suspected.[2] Zilucoplan should be withheld in patients who are undergoing treatment for meningococcal infections until the infection is resolved.[2] In addition, similar to other approved complement inhibitors, a REMS is necessary for zilucoplan to ensure the benefits outweigh the risks of serious meningococcal infections.

5.3.2. Other Infections

Given the potential increased susceptibility to other encapsulated bacterial infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, section 5 of labeling (warnings and precautions) will include the recommendation for vaccinating patients for the prevention of these infections according to ACIP guidelines.[2]

5.3.3. Pancreatitis and Other Pancreatic Conditions

In the RAISE study, adverse reactions of increased lipase and amylase were observed at higher rates with zilucoplan when compared to placebo (lipase: 6.9% vs 0%; amylase: 4.7% vs 1.1%).[42] The mean increase in lipase from baseline in the zilucoplan subjects was 44 U/L as compared to 2 U/L in the placebo group in the first two months of treatment.[42] Lipase levels exceeded three times the upper limit of normal in 7% of subjects treated with zilucoplan compared to no patients on placebo.[42]

Pancreatic adverse events did not occur in the 12-week placebo-controlled studies, however in the open-label extension studies (Study Pool S1B), 7 subjects (3.3%) receiving zilucoplan developed pancreatic conditions including pancreatitis in 4 of the subjects and pancreatic cysts in 3 of the subjects.[41] As previously mentioned in Section 5.1, there were two deaths from pancreatic adenocarcinoma in subjects receiving zilucoplan of which the clinical reviewer concluded that zilucoplan may have had a contributory role in acceleration of progression.[40]

Labeling will include the recommendation that patients be informed of this risk prior to starting zilucoplan therapy and that the prescriber should obtain lipase and amylase levels at baseline before starting treatment with zilucoplan. [40] In patients with suspected pancreatitis, zilucoplan should be discontinued and appropriate diagnostic evaluation should be initiated until pancreatitis is excluded or has resolved.[2]

6. Expected Postmarket Use

The Applicant has communicated that zilucoplan will be dispensed from a specialty pharmacy for chronic daily subcutaneous self-injection by the patient in an outpatient setting. Given the severe risk of meningococcal infection, it is important that patients are aware of the early signs and symptoms of infections, the need for vaccination, and the need to seek immediate medical attention when symptoms occur.

The most likely prescribers of zilucoplan are neurologists who are likely to have experience with the risks of complement inhibitors when managing patients with myasthenia gravis. However, as the different complement inhibitors affect different parts of the complement cascade, prescribers may not be aware of the differing risks and different vaccine requirements. Healthcare providers who prescribe zilucoplan will need to understand the risk of meningococcal infections associated with zilucoplan and actions to take to mitigate these risks.

7. Risk Management Activities Proposed by the Applicant

7.1. Review of Applicant's Proposed REMS

The proposed Zilbrysq REMS consists of ETASU that include prescriber certification (ETASU A), pharmacy certification (ETASU B), documentation of safe use conditions (ETASU D), an implementation system, and a timetable for submission of assessments of the REMS. Below is an overview of the Applicant's proposed REMS as amended and submitted on September 15, 2023.[1,26]

7.1.1. REMS Goals

The Applicant proposed the following:

The goal of the Zilbrysq REMS is to mitigate the risk of serious meningococcal infections.

1. Patients are vaccinated against meningococcal infections caused by Neisseria meningitidis serogroups A, C, W, Y (MenACWY) and serogroup B (MenB) prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed.
2. Patients are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.
3. Prescribers are aware of early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.

Reviewer's Comments: *When determining the goals and objectives for the REMS, we evaluated how zilucoplan will move through the drug use process, potential care gaps, and how the REMS will align with the primary public health goal which is to prevent meningococcal infections to the extent possible through the immunization of patients and if needed, antibacterial drug prophylaxis. Another public health goal for zilucoplan is identification of early signs and symptoms of meningococcal infection and the need for medical evaluation to mitigate the*

morbidity of infection should infection occur. The REMS objectives align with the public health prevention aims (primary and secondary prevention) and as written will allow a more objective assessment of the REMS.

The proposed goals and objectives of the REMS are acceptable.

7.1.2. REMS Elements

The Applicant proposed the following ETASU as part of the REMS requirements: prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe use conditions (ETASU D).

ETASU A: Prescriber certification

The Applicant proposed that a prescriber must certify in the Zilbrysq REMS prior to prescribing zilucoplan. To become certified, prescribers must review the prescribing information (PI), the *Healthcare Provider Safety Brochure*, *Patient Guide*, and *Patient Safety Card*. The prescriber must complete and submit the *Prescriber Enrollment Form* to the REMS.

Prior to initiating treatment with zilucoplan, prescribers must: 1) assess the patient for unresolved meningococcal infection, 2) assess the patient's vaccination status for meningococcal vaccines and vaccinate as needed according to current ACIP recommendations, 3) provide the patient with a prescription for antibacterial drug prophylaxis if the patient is not up to date with meningococcal vaccines and must start zilucoplan right away, and 4) counsel the patient using the *Patient Guide* and *Patient Safety Card*.

During treatment, prescribers must: 1) assess the patient for early signs and symptoms of meningococcal infection and evaluate immediately if infection is suspected, 2) withhold administration of zilucoplan if patients are being treated for meningococcal infection, and 3) revaccinate patients according to current ACIP recommendations.

Reviewer's Comments: *We agree with the requirement for prescriber certification (ETASU A). The prescriber certification requirement is similar to the prescriber certification requirement in the other complement inhibitors subject to a REMS. A REMS with ETASU A would ensure that prescribers are educated on the risk of serious meningococcal infections with zilucoplan and the need to counsel patients on this risk which supports the goal and objectives of the REMS. We additionally agree with the inclusion of the Prescriber Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, and Patient Guide to support prescriber education and patient counseling; and find these materials acceptable.*

ETASU B: Pharmacy Certification

The Applicant proposes that zilucoplan be dispensed only by certified pharmacies. Pharmacies must become certified by designating an authorized representative on the *Pharmacy Enrollment Form* who will coordinate REMS activities on behalf of the pharmacy, review training materials, enroll in the REMS, and ensure all relevant staff are trained in the REMS. If the authorized representative changes, the new authorized representative must re-enroll in the REMS in order to maintain certification.

ETASU D: Documentation of Safe Use Conditions

The Applicant proposed to include the following safe use conditions prior to the pharmacy dispensing zilucoplan. Before dispensing the first dose of zilucoplan, the pharmacy must verify the prescriber is certified through the processes and procedures established as a requirement of the REMS and contact the prescriber to assess and document the patient's vaccination status and/or need for antibacterial drug prophylaxis. For patients who are not up to date with meningococcal vaccines when starting treatment, the pharmacy must assess and document the patient's vaccination status for up to 6 months after the first dose of zilucoplan.

Reviewer's Comments: *We agree with the requirements for pharmacy certification and documentation of safe use conditions. These requirements are similar to the Empaveli REMS. The pharmacy will be required to look up the prescriber on the REMS website to verify the prescriber is certified prior to dispensing zilucoplan for every dispense and document this verification has occurred. The pharmacist will contact the prescriber prior to the first dispense and, if the patient's vaccination status is not up to date, for up to 6 months after the first dispense to assess and document the patient's vaccination status including antibacterial drug prophylaxis. The contact with prescribers will serve as a reminder to vaccinate if needed and documentation of vaccination and antibacterial drug prophylaxis will further inform if education and certification of prescribers results in appropriate vaccination of patients and therefore achieves the overall goal of the REMS. As the meningococcal vaccine series can take up to 6 months to complete, pharmacies must continue to assess patients through 6 months after the first dispense if the vaccination status for meningococcal vaccines is not up to date.*

While the pharmacist must contact the prescriber to assess and document the patient's vaccination status including antibacterial drug prophylaxis, pharmacies may continue to dispense without an updated vaccination history to avoid treatment delays for patients. Continued verification that a prescriber is certified in the REMS is a requirement for dispensing and must be completed prior to every dispense of zilucoplan. We agree with the inclusion of the Pharmacy Enrollment Form and find it acceptable.

7.1.3. Implementation System

Elements of an implementation system proposed by the Applicant to support REMS operations are listed in the REMS Supporting Document which include:

REMS Website

The Applicant proposes to maintain a *REMS website* to support prescriber and pharmacy ability to interface with the REMS and to enroll in the REMS online. REMS materials will be made available electronically by the Applicant through the website. The website will include a secure search tool for certified pharmacies to verify prescribers are certified prior to dispensing zilucoplan.

REMS Call Center

The Applicant proposes a REMS call center to provide REMS support to stakeholders. The call center staff will process prescriber and pharmacy enrollment forms received online, via fax, and via email, process requests for printed materials, respond to calls and address questions on the Zilbrysq REMS including tracking the number and reasons for the calls, identify potential adverse events, and manage/monitor compliance of all stakeholders in collaboration with the Applicant.

REMS Database

The Applicant proposes a validated, secure REMS database comprised of all REMS participants certified in the Zilbrysq REMS.

REMS Letter

The applicant proposes to annually send a reminder letter (*REMS Letter: Vaccination reminder to REMS certified prescribers*) to all REMS certified prescribers of zilucoplan to support prescriber awareness of the importance of verifying that patients' vaccination status is up to date according to the Advisory Committee on Immunization Practices recommendations.

***Reviewer's Comments**: We agree with the Applicant's proposal to include an implementation system. We had provided comments on June 2, 2023, August 24, 2023, and September 8, 2023, requesting clarifying information.[14,21,25] The Applicant has provided adequate detail in the REMS Supporting Document on pharmacy processes, the distribution model for zilucoplan, the REMS call center, and the REMS website. We agree with the inclusion of a REMS Letter and find the letter and website acceptable.*

7.1.4. Timetable for Submission of Assessments

The Applicant must submit REMS Assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS.

***Reviewer's Comments:** The Applicant had initially proposed submission of REMS Assessment Reports at 6 months,* (b) (4) *On June 16, 2023, the Applicant agreed to the Agency's recommended revisions for the REMS Assessment Reports to be submitted at 6 months, 12 months, and*

annually thereafter. The Supporting Document submitted on September 15, 2023 incorporated the Agency's recommended revisions for the assessment timetable and is acceptable.

7.1.5. REMS Materials & Key Risk Messages

Key Risk Messages

The Applicant proposed the following Key Risk Messages (KRM's) for the Zilbrysq REMS:

Healthcare Providers (HCPs):

1. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors; ZILBRYSQ is a complement inhibitor.
2. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Closely monitor patients for early signs and symptoms of meningococcal infections and evaluate immediately if infection is suspected.
3. Complete or update meningococcal vaccination (for serogroups A, C, W, and Y [MenACWY], and serogroup B [MenB]) at least 2 weeks prior to administering the first dose of ZILBRYSQ, according to current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccinations in patients receiving a complement inhibitor.
    - Because of inhibition of complement activity by ZILBRYSQ and risk of infection caused by nongroupable strains of Neisseria meningitidis, vaccination does not eliminate the risk of meningococcal infections, despite development of antibodies following vaccination.
    - If urgent ZILBRYSQ therapy is indicated in a patient who is not up to date with both MenACWY and MenB vaccines according to ACIP recommendations, administer meningococcal vaccine(s) as soon as possible and provide the patient with antibacterial drug prophylaxis.
4. Withhold administration of ZILBRYSQ in patients who are undergoing treatment for meningococcal infection until the infection is resolved.
5. Counsel patients using the **Patient Safety Card** and **Patient Guide**.
    - Counsel patients to carry the **Patient Safety Card** at all times during treatment and for 2 months after the last dose of ZILBRYSQ and to show the card to any healthcare provider that provides treatment.
    - Tell patients to seek immediate medical attention if they develop any of the following symptoms: headache with nausea, vomiting, stiff neck, stiff back, or fever; fever with or without a rash; sensitivity of eyes to light; confusion muscle aches with flu-like symptoms

Patients:

1. ZILBRYSQ increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections can be infections of the blood, linings of the brain, and spinal cord.
2. Meningococcal infections may become life threatening and cause death if not recognized and treated early.

3. Receive or update both meningococcal vaccines at least 2 weeks before your first dose of ZILBRYSQ or as soon as possible if you have not already had these vaccines.
4. If you have not completed vaccinations for meningococcal infections at least 2 weeks before your first ZILBRYSQ dose and ZILBRYSQ therapy must be started right away, take antibiotics as directed by your doctor.
5. Call your doctor or get emergency medical care right away if you get any signs or symptoms of a meningococcal infection. Signs and symptoms may include:
    - Headache with nausea, vomiting, stiff neck, stiff back, or fever; fever with or without a rash; sensitivity of eyes to light; confusion muscle aches with flu-like symptoms
6. Carry the **Patient Safety Card** with you at all times during treatment and for 2 months after your last dose of ZILBRYSQ. Show the card to any healthcare provider that treats you.

Reviewer's Comments*: In the July 31, 2023 amendment, the Applicant initially proposed KRM's that aligned with the REMS goal and objectives but did not address further REMS requirements and did not separate messages by stakeholder (healthcare provider vs patient).*[18] *In the September 15, 2023 amendment, the Applicant revised the KRM's in response to Agency comments sent on September 8, 2023 to include more detail related to specific measures taken to mitigate the risk of meningococcal infections and to list the messages separately for healthcare providers and patients.*[25,26] *The KRM's are included in section 3.2.5 REMS Key Risk Messages of the Supporting Document and are acceptable.*

REMS Materials

The Applicant included the following materials as part of the REMS submission:

- Prescriber Enrollment Form: serves to enroll prescribers in the REMS and for prescribers to attest they understand the requirements of the REMS as part of the process to become certified to prescribe zilucoplan.
- Pharmacy Enrollment Form: completed by the pharmacy's authorized representative on behalf of the pharmacy to enroll in the REMS. The authorized representative attests they understand the requirements of the REMS as part of the process to become certified to dispense and will train staff on the REMS requirements.
- Healthcare Provider Safety Brochure: serves to inform prescribers and pharmacy staff of the risks of serious meningococcal infections with zilucoplan, REMS requirements, and the responsibilities of the prescriber and pharmacies.
- Patient Safety Card: Prescribers provide this to the patient and instruction the patient to carry the card with them at all times for the duration of treatment and for 2 months after the last dose of zilucoplan. The patient should present the card to treating healthcare provider if the patient experiences any signs or symptoms of meningococcal infection. Serves to inform any healthcare provider treating the patient that the patient is receiving a complement inhibitor. It also includes the risk of serious meningococcal infections, signs and symptoms of meningococcal infections, and to discontinue zilucoplan if meningococcal infection is suspected.
- Patient Guide: serves to inform patients of the risk of serious meningococcal infections with zilucoplan, the need for both meningococcal vaccinations (MenACWY and MenB),

the need to take antibiotics as directed by the prescriber, and the signs and symptoms of meningococcal infection.

- REMS Letter: Vaccination reminder to REMS certified prescribers: annual reminder letter issued to all REMS certified prescribers of zilucoplan to ensure prescriber awareness of the importance of verifying that patients' vaccination status is up to date according to the Advisory Committee on Immunization Practices recommendations including the need for vaccine boosters.
- REMS Website: serves as a source of information for stakeholders and part of the implementation system for the Applicant. It allows prescribers and pharmacies to enroll in the REMS online. The website will include a secure lookup of certified prescribers to be used by certified pharmacies to verify prescriber certification. The REMS materials will be available on the website and downloadable in an electronic format.

***Reviewer's Comments**: We agree with the Applicant's proposed REMS materials and find them to be acceptable.*

7.1.6. Supporting Document

The REMS Supporting Document includes the Applicant's rationale for the REMS and how the REMS will be implemented (e.g., proposed distribution model, confirmation that a prescriber is certified, process for pharmacy assessment and documentation of patient vaccination status including antibacterial drug prophylaxis prior to dispensing). It also contains the key risks messages for the various stakeholders.

***Reviewer's Comments:** The Applicant clarified the prescriber verification process. The pharmacy authorized representative will log in to the REMS web portal to search for the prescriber in the prescriber look-up tool and check that the prescriber is certified. Only the authorized representative will be able to create a log-in on the REMS website and the Applicant clarified that there can be multiple authorized representatives for a single certified pharmacy. There is not an authorization code generated for each dispense of zilucoplan. If there are access issues to the web portal, the authorized representative can call the REMS call center to obtain verbal verification. The pharmacy will maintain records of the proof of verification of prescriber certification.*

The Applicant clarified the process for pharmacy assessment of patient vaccination status including antibacterial drug prophylaxis prior to dispensing. The documentation of the patient's vaccination status and antibacterial drug prophylaxis will be maintained by the pharmacy as part of the patient's profile in the pharmacy system.

The Applicant has clarified how the REMS will be implemented and assessed; the Supporting Document is acceptable.

7.1.7. Noncompliance

The Applicant included a noncompliance plan in their June 16, 2023, submission and their latest submission on September 15, 2023. The Applicant's submissions did not include an audit plan.

***Reviewer's Comments**: The Agency did not provide comments on the submitted noncompliance plan. The Applicant is to submit their full audit and noncompliance plan within 60 days post approval as a REMS Methodology for Agency review.*

7.1.8. REMS Assessment Plan

The proposed REMS Assessment Plan is included in the REMS Supporting Document, which was submitted on August 31, 2022, amended on November 14, 2022, and revised on June 16, 2023, August 4, 2023, August 29, 2023, and September 15, 2023.

The proposed REMS Assessment Plan includes metrics under the following categories: Program Outreach and Communication, Program Implementation and Operations, Safe Use Behaviors, Health Outcomes and/or Surrogates of Health Outcomes, Knowledge, and an Overall Assessment of REMS Effectiveness. The REMS Assessment Plan includes metrics to inform the outcome and process key performance indicators (see Section 8), that if met, would indicate that the REMS is meeting its goal.

***Reviewer's Comments:** The REMS Assessment Plan was designed to evaluate whether the REMS is meeting its goal of mitigating the risk of serious meningococcal infection, to evaluate if the REMS is being implemented and functioning as intended, to determine if stakeholders are compliant with REMS requirements and to assess any unintended burden on the healthcare system or issues with patient access. Knowledge, attitude, and behavior (KAB) surveys will be conducted that will determine whether prescribers and patients are aware of the importance of completing vaccinations prior to treatment initiation, the early signs and symptoms of meningococcal infection, and the need for immediate medical evaluation. These KAB survey results will be submitted beginning with the 12-month REMS Assessment Report as there is insufficient time for the KAB survey protocols to be reviewed by the Agency and have the Applicant conduct the surveys by the data cutoff for the 6-month REMS Assessment Report.*

During the review of the application, the Agency provided comments and edits on July 27, 2023[17] August 24, 2023[21] and September 8, 2023[25]. The Applicant has addressed all of our comments on the REMS Assessment Plan and it is acceptable. The final and agreed upon REMS Assessment Plan is included in the Appendix of this review and will be included in the Zilbrysq Approval Letter.

7.1.9. Summary of OPDP Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on July 12, 2023 to provide feedback on the content of the *Prescriber Enrollment Form, Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Vaccination Reminder to REMS Certified Prescribers,*

Patient Safety Card, Patient Guide, and Zilbrysq REMS Website. The OPDP review was completed by Roseline Boateng, Regulatory Review Officer, OPDP on August 2, 2023.

The OPDP recommendations are summarized below.

- Align the language in the REMS materials with the fully approved indication from the Prescribing Information (PI), and the final approved Medication Guide (MG).
- Revise the risk information on confusion (b) (4) in the *Healthcare Provider Safety Brochure, Patient Safety Card,* and *Patient Guide,* to be consistent with the PI.
- Fix a graphic blocking the space for the "Emergency Contact Number" in the *Patient Safety Card.*
- Throughout several REMS materials, update language to be consistent with the PI.

DRM accepted all the recommendations and provided them to the Applicant on August 24, 2023.[21] The Applicant incorporated all edits in their September 15, 2023 REMS amendment.[26]

8. Discussion

Discussion of the Need for a REMS

The benefits of treatment of gMG with zilucoplan were demonstrated in a Phase 3, multicenter, randomized, double-blind, placebo-controlled study. In the zilucoplan treatment group, there were statistically significantly greater decreases in MG-ADL total score and QMG total score at Week 12 when compared with placebo. The clinical reviewer recommends approval of zilucoplan for treatment of gMG in adult patients who are anti-acetylcholine receptor antibody positive on the basis of the efficacy and safety information currently available.[40]

Although there have been no reported cases to date of serious meningococcal infections in the clinical development program for zilucoplan, all study subjects were required to be vaccinated against meningococcal infections at the time of initiating study treatment and receive antibacterial drug prophylaxis if needed. The risk of serious meningococcal infections is a known risk for Soliris and Ultomiris; both are complement C5 inhibitors and are subject to a REMS to mitigate the is risk of serious meningococcal infections. Inhibition of the terminal complement system leads to increased susceptibility to serious meningococcal infections.

The review team determined that a REMS is necessary to ensure the benefits of treatment with zilucoplan outweigh the risks of serious meningococcal infection.

The three ETASU of the REMS (prescriber certification, pharmacy certification, and documentation of safe-use condition [vaccines or antibacterial drug prophylaxis]) are necessary in combination to form a program that will mitigate the risks of serious meningococcal infection and provide data to assist in determining if the goals of the program are being met. The design of this REMS is similar to Empaveli (pegcetacoplan) and more closely aligns with the Agency's current thinking on the ETASU that are necessary to ensure safe use for complement inhibitors.

Prescriber certification ensures that prescribers are knowledgeable about the risk of meningococcal infection associated with complement C5 inhibitors, the need to provide the appropriate vaccines against meningococcal infections prior to zilucoplan initiation, and the need for antibacterial drug prophylaxis if zilucoplan is initiated prior to the patient being up to date on meningococcal vaccines. Prescribers also attest to counsel patients about the signs of symptoms of meningococcal and when patients should seek additional medical attention. Pharmacy certification ensures that dispensing pharmacy staff is trained about the risk of meningococcal infection and assess the patient vaccination status and documents the findings. This will assist in assessing if the REMS goals are being accomplished. While we ideally would like all patients to be vaccinated, we recognize that some patients may decline vaccination or be unable to be vaccinated; therefore 100% compliance with vaccination is not reasonable for this particular drug.

The proposed REMS for zilucoplan as well as other products that are complement inhibitors were shared with the REMS Oversight Committee (ROC)[j] on August 15, 2023. The members of the ROC did not raise any concerns about the planned strategy for zilucoplan.

Assessment of the REMS and Key Performance Indicators

Key Performance Indicators (KPIs) are measures that are essential in determining whether the REMS is achieving its goal of mitigating the risk of serious meningococcal infection. The KPIs have been established by developing a minimum target threshold for specific assessment metrics that indicate if the REMS is functioning as designed and may help determine if modifications to the REMS are necessary. A KPI at or below the established minimum threshold indicates that the REMS is not functioning as expected and may require a modification to meet the goals of the REMS. The Applicant may also need to conduct a root cause analysis (RCA) or deploy corrective and preventative actions (CAPAs) if the KPI is below the target threshold.

Although mitigation of meningococcal infections is an overall goal of the REMS, life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors, therefore it may not be possible to prevent all cases of serious meningococcal infection. While the number of cases of serious meningococcal infection will be measured and assessed, this will not be a KPI to assess the success of the REMS. The REMS provides training to prescribers and is intended to affect safe use behavior so prescribers do not start treatment in patients with an unresolved meningococcal infection, patient vaccine status is assessed and patients receive required meningococcal vaccines prior to initiating treatment with zilucoplan, and patients receive antibacterial drug prophylaxis if the patient must start therapy urgently before the vaccinations are up to date. To align the KPIs with the objectives of the REMS, the KPIs are related to meningococcal vaccination rates and education of prescribers (achieved through prescriber certification).

[j] As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

The KPIs for zilucoplan are the following:

1) Percentage (%) of patients dispensed Zilbrysq who received the first dose of meningococcal vaccines (MenACWY and MenB) and antibacterial drug prophylaxis if needed before the first dispense
2) Percentage (%) of Zilbrysq dispenses corresponding to prescriptions written by REMS certified Healthcare Providers

Over the course of the review, DRM, DMAMES, DN1, and OMEPRM discussed and revised the KPIs to be specific and to align with the objectives of the REMS. DRM and DMAMES discussed determining the KPI metrics and target thresholds, and how the data would be captured for the KPIs.

The patient vaccination KPI is an outcome indicator which aligns with the primary objective of the REMS and corresponds with the strategy to directly affect safe use behavior. While the boxed warning and Section 5 of the label indicate that a patient must have up to date meningococcal vaccinations prior to receiving zilucoplan, not all patients will have completed the vaccine series at the time of the first dispense as some patients must start zilucoplan urgently. We also note that some patients may refuse vaccinations. Therefore, it was determined that evaluating the percentage of patients dispensed zilucoplan who received the first dose of meningococcal vaccines and antibacterial drug prophylaxis if needed before the first dispense was more appropriate and reflected the minimum expectation for vaccination prior to the first dispense. The data for this metric will be documented by the pharmacy as part of the processes and procedures to assess the patient's vaccination status for up to date meningococcal vaccines including antibacterial drug prophylaxis if needed by contacting the prescriber. The data will be obtained via assessment reports and audits of the certified pharmacy.

The KPI threshold (80%) for the outcome indicator was derived based on experience with the assessment results for related products with approved REMS in this therapeutic class, we also considered the removal (b) (4) , the design of the REMS not requiring vaccination as a hard stop for dispensing, how the data will be collected by the pharmacy and the potential for missing data at the time of the first dispense, and the national rates of compliance for other vaccine schedules.[48-50] Therefore, we consider 80% a reasonable minimum target threshold for this KPI.

The KPI related to prescriber certification is a process indicator which corresponds with the strategy to directly affect knowledge. This KPI applies to all three of the REMS objectives as prescriber education is a strategy for each of the REMS objectives (education on importance of vaccination, signs and symptoms of meningococcal infection, and need for medical evaluation). Including a process indicator will help assess whether the REMS is functioning as intended. The data for this metric will be documented by the pharmacy as part of the processes and procedures to verify the prescriber is certified before dispensing zilucoplan. The data will be obtained via assessment reports and audits of the certified pharmacy.

The KPI threshold (99%) for the prescriber certification KPI is based on the pharmacy verification of prescriber certification being a closed system and compliance rates with closed systems in other REMS. Although Zilbrysq REMS is a closed system, where pharmacy verification of vaccination status including antibacterial drug prophylaxis is required prior to dispensing, there is still opportunity for human error

as these actions are not built into the pharmacy system and pharmacists must step outside their typical workflow to confirm prescriber certification or document patient vaccination status. Therefore, the proposed REMS relies on the pharmacy authorized representative to ensure that processes and procedures are developed and there is good compliance. As described in a the "Improving the Reliability of Health Care" white paper from the Institute of Healthcare Improvements (IHI) the expected failure rate in a system that has process in place, which includes an identification trigger to help identify and mitigate failure such as a healthcare setting or pharmacy identifying patients that are not vaccinated per ACIP recommendations, will help move the reliability of the care process to 10^{-2}.[51] Therefore, the expected failure rate is very low and a high threshold of 99% is achievable, appropriate, and in line with the expected reliability of 10^{-2}. Therefore, we consider 99% a reasonable minimum target threshold for this KPI.

DRM concludes that based on the review of the proposed REMS received on September 15, 2023, the REMS will support actions that will mitigate the risk of serious meningococcal infection.[26]

9. Conclusion & Recommendations

The risk of serious meningococcal infections associated with complement C5 inhibitors, such as zilucoplan, is significant and it is necessary for prescribers, pharmacists, and patients to understand this risk and the need to complete or update meningococcal vaccination at least 2 weeks prior to initiating treatment with zilucoplan and antibacterial drug prophylaxis if needed before initiation of zilucoplan if the risk of delaying treatment outweighs the risk of meningococcal infection. Based on the severity of the risk, DRM and DN1 agree that requiring a REMS consisting of prescriber certification, pharmacy certification, and documentation of safe use conditions (pharmacy assessment and documentation of meningococcal vaccination and antibacterial drug prophylaxis prior to dispensing) is necessary to ensure that the benefits outweigh the risks. The REMS will also include an implementation system and timetable for submission of assessments.

DRM finds the Applicant's proposed Zilbrysq REMS received on September 15, 2023, to be acceptable and it is appended to this review.

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21. Matthews, M. Zilbrysq (zilucoplan) proposed REMS Interim Comments. NDA 216834. August 24, 2023.
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11. Appendix

Assessment Plan
REMS Document
Prescriber Enrollment Form
Pharmacy Enrollment Form
Healthcare Provider Safety Brochure
Patient Safety Card
Patient Guide
REMS Letter: Vaccination reminder to REMS certified prescribers
REMS Website

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/

SARAH K HOLMAN
10/12/2023 03:47:29 PM

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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	NDA
Application Number	216834
PDUFA Goal Date	December 1, 2023
Nexus TTT#	2022-1164
Reviewer Names	Sarah K. Holman, PharmD, BCPS (DRM) Anahita Tavakoli, MA (DRM) Judine Berlus, PharmD, MPH Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Team Leaders	Barbara Bergquist, PharmD (DMAMES) Jacqueline Sheppard, PharmD (DRM)
Division Director	Cynthia LaCivita, PharmD (DRM)
Review Completion Date	September 8, 2023
Subject	Interim Review of Proposed REMS
Established Name	Zilucoplan
Trade Name	Zilbrysq
Name of Applicant	UCB, Inc.
Therapeutic Class	Complement C5 inhibitor
Formulation	Subcutaneous injection solution 40 mg/mL (single-use prefilled syringe)
Dosing Regimen	

Body Weight	Once Daily SubQ Dosage
Less than 56 kg	16.6 mg
56 kg to less than 77 kg	23 mg
≥77 to <150 kg	32.4 mg

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Zilbrysq (zilucoplan), New Drug Application (NDA) 216834, submitted by UCB, Inc. (hereafter referred to as the Applicant) on August 31, 2022 and amended on November 14, 2022, June 16, 2023, July 31, 2023, and August 29, 2023.[1-5]

Zilbrysq is a complement protein 5 (C5) inhibitor proposed for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive.[6] This application is under review in the Division of Neurology 1 (DN1).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system (IS), and a timetable for submission of assessments to ensure the benefits of zilucoplan outweigh the risk of serious meningococcal infections.

This interim review provides comments on the August 29, 2023 REMS amendment. In this amendment, the Applicant proposed changes to the REMS Document and REMS materials in response to the Agency comments sent on August 24, 2023.[7]

The proposed changes to the REMS include:

- REMS Document
  - Updated REMS goals and objectives to incorporate the Agency's recommended edits
  - Revised the participant requirements to align with the revisions to the label sent to the Applicant on August 24, 2023 and to incorporate Agency edits as relates to pharmacy requirements
  - Added language to prescriber requirements before treatment initiation related to instructions for patients regarding carrying the Patient Safety Card
  - Changed adverse event reporting method for pharmacies to be via email (b) (4)
- Prescriber Enrollment Form, Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, Patient Guide, and REMS Letter: Vaccination reminder to REMS certified prescribers
  - Updated to reflect changes made to the REMS Document and the Agency revisions to the label, and to incorporate the Agency's recommended edits
  - Throughout the materials, revised the name of the "Patient (b) (4)" to "Patient Guide"
  - Revised language in the Healthcare Provider Safety Brochure and in the Patient Guide to reflect the Applicant's proposed revisions to the label submitted on August 29, 2023 regarding whether vaccinations should be "completed" or (b) (4) at least 2 weeks before the first dose of zilucoplan
  - Changed adverse event reporting method for pharmacies to be via email
  - Removed language (b) (4) in Healthcare Provider Safety Brochure in statement outlining meningococcal infection risk
- REMS Website
  - Updated to reflect Agency revisions to the label, REMS Document, and REMS materials
  - Clarified that a single certified pharmacy can have multiple Authorized Representatives that would each create a separate website login; other pharmacy staff of the certified pharmacy will not be able to verify prescriber certification

- Supporting Document
    - Revised to align with changes made to the REMS Document
    - Added language related to pharmacy processes including information for how the pharmacy will follow up with prescribers to obtain missing data on vaccination status and antibacterial drug prophylaxis
    - Added language related to the distribution model for zilucoplan
    - Revised the Assessment Plan to align with Agency edits
    - Revised the key performance indicator (KPI) and associated target thresholds

2. Regulatory History

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

- **08/24/2023**: A draft label was sent to the Applicant that included the Agency's revisions to language pertaining to meningococcal vaccination and antibacterial drug prophylaxis.[8]
- **08/24/2023**: Interim comments issued to the Applicant. Agency provided revisions of the REMS goal and objectives, revisions to the REMS Document and materials to align with Agency labeling revisions, and updates to the key performance indicators and associated thresholds.[7]
- **08/29/2023**: Applicant submitted draft label and REMS materials with proposed revisions.[9]
- **08/30/2023:** Major amendment acknowledgement letter sent to the Applicant due to labeling and REMS deficiencies; PDUFA goal date extended by 3 months.[10]

3. Review of Applicant's Proposed REMS

3.1. REMS Goals

The Applicant proposed to revise the REMS goal and objectives to the following to align with Agency edits:

(b) (4) The goal of the Zilbrysq REMS is to mitigate the risk of serious meningococcal infection.

(b) (4)

1) Patients are vaccinated against meningococcal infection caused by Neisseria meningitidis serogroups A, C, W, Y (MenACWY) and serogroup B (MenB) prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed
2) Patients are aware of the early signs and symptoms of meningococcal infection and the need for immediate medical evaluation
3) Prescribers are aware of the early signs and symptoms of meningococcal infection and the need for immediate medical evaluation

Reviewer comments:

These changes to the REMS goal and objectives are acceptable.

3.2. REMS Document

The Applicant incorporated the Agency's requested changes to the REMS Document including revisions to align with revisions to the label sent to the Applicant on August 24, 2023.[8]

Reviewer comments:

These changes to the REMS Document are acceptable except as noted below.

3.3. REMS Requirements

3.3.1. REMS Participant Requirements

The Applicant incorporated the Agency's requested changes to the Healthcare Provider, Patient, and Pharmacy requirements of the REMS Document to align with updated labeling. The Applicant proposed the following additional revisions to the prescriber requirements before treatment initiation:

- Added in bullet 7, "For patients who are not up to date with MenACWY and MenB vaccines at least two weeks prior to initiation of treatment and who must start Zilbrysq urgently:…"
- Added a bullet: "(b) (4) the patient to carry the Patient Safety Card at all times during and for 2 months following treatment with Zilbrysq"

Reviewer comments:

The change to add language, "who", to bullet 7 is acceptable. Addition of language regarding (b) (4) the patient to carry the Patient Safety Card is acceptable, however this language should be revised to combine with the preceding bullet.

3.3.2. REMS Applicant Requirements

3.3.2.1. Operations

The Applicant incorporated the Agency's requested changes in the Applicant requirements to support REMS operations including the following:

- Removed language in bullet 7 to (b) (4) obtain required data regarding reports of meningococcal infection
- Changed (b) (4) to "database" in bullets 12 and 13 to align with the Technical Conformance Guide

The Applicant proposed the following additional revisions to the Applicant requirements to support REMS operations:

- In bullet 1, revised the second sentence to "REMS website must include the capability (b) (4) for prescribers and pharmacies to enroll in the REMS online, by fax, or by email…"
- In bullet 6, revised to "Ensure prescribers (b) (4) are able to report adverse events suggestive of meningococcal infection by phone (b) (4) pharmacies are able to report (b) (4) by email.

Reviewer comments:

These changes to the Applicant requirements to support REMS operations are acceptable, however the following revision is necessary.

- *Revise bullet 6 to separate prescriber and pharmacy adverse event reporting methods into two separate bullets for clarity.*

3.3.2.2. Compliance

The Applicant incorporated the Agency's requested changes in the Applicant requirements to ensure REMS participants' compliance with the REMS including edits to the audit timeframe for wholesalers, distributors, and other entities that distribute Zilbrysq to revise the language from (b) (4) to "no later than" (b) (4) calendar days after their first commercial distribution of Zilbrysq.

Reviewer comments:

These changes to the Applicant requirements to ensure REMS participants' compliance with the REMS are acceptable, however the audit timeframe for certified pharmacies, wholesalers, distributors, and other entities that distribute Zilbrysq should be revised to 180 days to align with audit timeframes for similar REMS.

The Applicant should revise bullet 18 to the following: "Audit certified pharmacies no later than (b) (4) 180 calendar days from the date the first shipment was sent from the pharmacy, then annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements."

The Applicant should revise bullet 19 to the following: "Audit wholesalers, distributors, and other entities that distribute ZILBRYSQ no later than (b) (4) 180 calendar days after their first commercial distribution of ZILBRYSQ and annually thereafter to ensure all REMS processes and procedures are in place, functioning, and comply with REMS requirements."

3.3.3. REMS Materials

The Applicant incorporated the changes to the labeling sent to the Applicant on August 24, 2023 to the Prescriber Enrollment Form, Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, Patient Guide, and REMS Letter: Vaccination reminder to REMS certified prescribers.[7,8] In addition, the materials were further revised by the Applicant as follows:

Prescriber Enrollment Form

- Added the following language to the section on requirements before treatment initiation: "Assess the patient's vaccination status for (b) (4) meningococcal serogroups A, C, W, and Y (MenACWY) and serogroup B (MenB) and vaccinate as needed according to the current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccinations in patients receiving a complement inhibitor."

Pharmacy Enrollment Form

- Revised the third bullet under the Authorized Representative Attestations to the following: Establish processes and procedures to verify the prescriber is certified and document ~~the~~ findings.

Healthcare Provider Safety Brochure

- Revised the language under the heading "Risk of Meningococcal Infections" to the following: "Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors~~,~~ (b) (4)
- In the first bullet on the second page, changed "complete" to (b) (4) and added "both" before listing the types of vaccines required

- Added the following language to second bullet on the second page and on the fourth page under the heading "During Zilbrysq treatment": (b) (4)
- On the fourth page regarding patient counseling points, changed "complete" to (b) (4) before listing the meningococcal vaccines required
- On the sixth page under pharmacy requirements at all times, revised the adverse event reporting method for pharmacies to be "by email at ds.usa@ucb.com."

Patient Guide

- Revised the first bullet under "Getting your Meningococcal Vaccines" to the following: "~~Complete~~ (b) (4) or update two types of meningococcal vaccines (for both serogroup B and serogroup A, C, W, and Y infections) at least 2 weeks before your first dose of Zilbrysq if you have not already had these vaccines."
- Revised (b) (4) to the following: "If your doctor decides that urgent treatment with Zilbrysq is needed and you have not (b) (4) ~~completed~~ or updated vaccinations…"

Reviewer comments:

We find the changes to the Patient Safety Card and REMS Letter: Vaccination reminder to REMS certified prescribers acceptable.

We do not agree with the Applicant's proposed changes to the Prescriber and Pharmacy Enrollment Forms. The prescriber attestations and authorized representative attestations should align with the language in the REMS Document.

We do not agree with the Applicant's proposed changes to the Healthcare Provider Safety Brochure and Patient Guide as related to changing "complete" to (b) (4) or (b) (4) regarding vaccinations 2 weeks prior to the first dose of Zilbrysq. The Applicant should align the REMS materials with the Agency revisions to the label and Medication Guide sent on September 8, 2023. See attached redlined materials for reference.

REMS Website

The Applicant incorporated the changes requested in Agency comments on August 24, 2023 to the REMS website.[7] The Applicant additionally modified the placement of the product name in the header, updated the copyright date in the footer, and updated the zip code in the footer.

The Applicant provided a response to the Agency's inquiry of how pharmacy staff will log-in on the website to verify prescriber certification as the website currently only has the capability for the Authorized Representative to create a log-in. The Applicant stated that a single certified pharmacy can have multiple Authorized Representatives and each Authorized Representative will have a separate log-in; other pharmacy staff will not be able to verify prescriber certification in the REMS.

Reviewer comments:

We find the changes to the REMS website acceptable. However, the following revisions to the REMS website are necessary:

- *On page 1.1 Home Page, the Applicant should revise the text in the box titled "Patients" to the following: "Receive or update both meningococcal vaccines prior to starting ZILBRSYQ therapy as directed by your prescriber. Understand the need for immediate*

*medical attention for any signs or symptoms of meningococcal infection. Carry the **Patient Safety Card** at all times during treatment and for 2 months after your last ZILBRSYQ dose."*

- *We have concerns that there will be multiple Authorized Representatives for a single certified pharmacy. Clarify how the Applicant will ensure there is always an individual at the certified pharmacy during operating hours that has access to log in to the REMS website and verify prescriber certification.*

4. Supporting Document

The Applicant incorporated the Agency's requested changes to the Supporting Document including the following:

- Added details related to pharmacy processes and the distribution model for zilucoplan
- Revised antibiotic prophylaxis to "antibacterial drug prophylaxis" throughout
- Updated the Supporting Document to align with changes to the REMS Document

Reviewer comments:

We find the changes to the Supporting Document acceptable, however the following revisions are recommended.

- *The following statements are unclear:* (b) (4)
  - *The REMS Document does not explicitly state that Healthcare Providers are required to provide information on patient vaccination status to the pharmacy. In addition, the Healthcare Provider is contacted by the certified pharmacy for patient vaccination status information and this information is not provided directly to the REMS.*
  - *Recommend revision to these statements for clarity to the following: "Healthcare providers will be asked to provide details to the certified pharmacy on a patient's vaccination status. The certified pharmacy will assess and document a patient's vaccination status based on the information provided by the certified Healthcare Provider."*

4.1. Key Risk Messages

The Applicant did not propose any revisions to the REMS Key Risk Messages (KRM's) that were submitted on July 31, 2023.[4]

Reviewer comments:

We do not find the proposed REMS Key Risk Messages (KRM's) acceptable. The KRM's should include more detail related to specific measures taken to mitigate the risk of meningococcal infections and should be listed separately for healthcare providers and patients. The Applicant should incorporate the Agency's revisions to the KRM's into section 3.2.5 REMS Key Risk Messages in the Supporting Document. We have revised the KRM's to the following:

Healthcare Providers (HCPs)

1. *Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors; ZILBRYSQ is a complement inhibitor.*
2. *Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Closely monitor patients for early signs and symptoms of meningococcal infections and evaluate immediately if infection is suspected.*
3. *Complete or update meningococcal vaccination (for serogroups A, C, W, and Y [MenACWY], and serogroup B [MenB]) at least 2 weeks prior to administering the first dose of ZILBRYSQ, according to current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccinations in patients receiving a complement inhibitor.*
    - *Because of inhibition of complement activity by ZILBRYSQ and risk of infection caused by nongroupable strains of Neisseria meningitidis, vaccination does not eliminate the risk of meningococcal infections, despite development of antibodies following vaccination.*
    - *If urgent ZILBRYSQ therapy is indicated in a patient who is not up to date with both MenACWY and MenB vaccines according to ACIP recommendations, administer meningococcal vaccine(s) as soon as possible and provide the patient with antibacterial drug prophylaxis.*
4. *Withhold administration of ZILBRYSQ in patients who are undergoing treatment for meningococcal infection until the infection is resolved.*
5. *Counsel patients using the **Patient Safety Card** and **Patient Guide**.*
    - *Counsel patients to carry the **Patient Safety Card** at all times during treatment and for 2 months after the last dose of ZILBRYSQ and to show the card to any healthcare provider that provides treatment.*
    - *Tell patients to seek immediate medical attention if they develop any of the following symptoms: headache with nausea, vomiting, stiff neck, stiff back, or fever; fever with or without a rash; sensitivity of eyes to light; confusion muscle aches with flu-like symptoms*

Patients

1. *ZILBRYSQ increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections can be infections of the blood, linings of the brain, and spinal cord.*
2. *Meningococcal infections may become life threatening and cause death if not recognized and treated early.*
3. *Receive or update both meningococcal vaccines at least 2 weeks before your first dose of ZILBRYSQ or as soon as possible if you have not already had these vaccines.*
4. *If you have not completed vaccinations for meningococcal infections at least 2 weeks before your first ZILBRYSQ dose and ZILBRYSQ therapy must be started right away, take antibiotics as directed by your doctor.*
5. *Call your doctor or get emergency medical care right away if you get any signs or symptoms of a meningococcal infection. Signs and symptoms may include:*
    - *Headache with nausea, vomiting, stiff neck, stiff back, or fever; fever with or without a rash; sensitivity of eyes to light; confusion muscle aches with flu-like symptoms*

6. *Carry the **Patient Safety Card** with you at all times during treatment and for 2 months after your last dose of ZILBRYSQ. Show the card to any healthcare provider that treats you.*

4.2. REMS Assessment Plan

The Applicant proposed changes to the Zilbrysq REMS Assessment Plan included in the REMS Supporting Document submitted on August 29, 2023. The Applicant revised Safe Use Behavior metrics 7b and 7ei to remove the word "completed". For metric 7b the Applicant replaced "completed" with (b) (4) and for metric 7ei they replaced "completed" with (b) (4) The Applicant's rationale for the revisions was to align with their proposed changes to the Zilbrysq label and the Medication Guide. The Applicant also proposed minor editorial changes to metrics to assess Health Outcomes and/or Surrogates of Health Outcomes.

REMS Assessment Analyst comments:

We do not agree with all the proposed changes to the REMS Assessment Plan submitted on August 29, 2023. The Applicant is to update metrics 7b and 7ei to include "completed" vaccinations to align with the revised label sent on September 8, 2023. We agree with the Applicant's minor editorial changes to the Health Outcome metrics. Refer to the Appendix for the revised REMS Assessment Plan. Our recommended revisions for the REMS Assessment Plan are included in the Comments to the Applicant found in Section 7 of this review.

5. Key Performance Indicators

The Applicant incorporated the Agency's requested changes to the key performance indicators (KPI) and their associated target thresholds as follows:

- KPI #1: Percentage (%) of patients dispensed Zilbrysq who received the first dose of meningococcal vaccines (MenACWY and MenB) and antibacterial drug prophylaxis if needed before the first dispense (b) (4)
    - Proposed target threshold: 80%
    - Rationale: Based on robust REMS design, including educational materials and an assessment of the patient's vaccination status including antibacterial drug prophylaxis, if appropriate, before first ZILBRYSQ dispense, the percentage of patients dispensed ZILBRYSQ who received the first dose of meningococcal vaccines (MenACWY and MenB) and antibacterial drug prophylaxis if needed, before the first dispense is anticipated to be very high and notably higher than what is observed for other recommended age-appropriate vaccines in the US which show a low compliance rate based on composite measures (Centers for Disease Control and Prevention [CDC], 2023).
- KPI #2: Percentage (%) of Zilbrysq dispenses (b) (4) corresponding to prescriptions written by REMS certified Healthcare Providers
    - Proposed target threshold: 99%
    - Rationale: Based on the robust REMS design, including verification of HCP certification before each dispense, the percentage of ZILBRYSQ dispensations corresponding to prescriptions written by REMS certified HCPs is anticipated to be very high.

Reviewer comments:

We find the KPI and associated target thresholds proposed by the Applicant acceptable. The Applicant should adjust the rationale for the KPI #1 target threshold to reflect the lower target threshold of 80%.

6. Conclusions and Recommendations

DRM does not find the proposed REMS for Zilbrysq (zilucoplan) as submitted on August 31, 2022, and last amended on August 29, 2023, to be acceptable, as described in this review. Send the comments in Section 7 to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within 5 business days.

7. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on August 31, 2022, last amended on August 29, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

REMS Document

The following revisions are necessary to the REMS Document. See the attached redlined document for reference.

- In prescriber requirements before treatment initiation, addition of language regarding (b) (4) the patient to carry the Patient Safety Card is acceptable, however revise this language to combine with the preceding bullet.
- In Applicant requirements to support REMS operations, bullet 6 regarding adverse event reporting: Separate prescriber and pharmacy adverse event reporting methods into two separate bullets.
- Revise bullet 18 to the following: "Audit certified pharmacies no later than (b) (4) 180 calendar days from the date the first shipment was sent from the pharmacy, then annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements."
- Revise bullet 19 to the following: "Audit wholesalers, distributors, and other entities that distribute ZILBRYSQ no later than (b) (4) 180 calendar days after their first commercial distribution of ZILBRYSQ and annually thereafter to ensure all REMS processes and procedures are in place, functioning, and comply with REMS requirements."

Prescriber Enrollment Form, Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, Patient Guide, and REMS Letter: Vaccination reminder to REMS certified prescribers

We agree with the proposed changes to the Patient Safety Card and REMS Letter: Vaccination reminder to REMS certified prescribers.

We do not agree with the Applicant's proposed changes to the Prescriber Enrollment Form and Pharmacy Enrollment Form. The prescriber attestations and authorized representative attestations should align with the language in the REMS Document. See attached redlined materials for reference.

We do not agree with the Applicant's proposed changes to the Healthcare Provider Safety Brochure and Patient Guide as related to changing "complete" to (b) (4) or (b) (4) regarding vaccination 2 weeks prior to the first dose of Zilbrysq. Align the Healthcare Provider Safety Brochure and Patient Guide with

the Agency revisions to the label and Medication Guide sent on September 8, 2023. See attached redlined materials for reference.

REMS Website

We find the changes to the REMS website acceptable. However, the following revisions to the REMS website are necessary:

- On page 1.1 Home Page, revise the box titled "Patients" to the following: "Receive or update both meningococcal vaccines prior to starting ZILBRSYQ therapy as directed by your prescriber. Understand the need for immediate medical attention for any signs or symptoms of meningococcal infection. Carry the **Patient Safety Card** at all times during treatment and for 2 months after your last ZILBRSYQ dose."
- We have concerns that there will be multiple Authorized Representatives for a single certified pharmacy. Clarify how the Applicant will ensure there is always an individual at the certified pharmacy during operating hours that has access to log in to the REMS website and verify prescriber certification.

Supporting Document

We find the changes to the Supporting Document acceptable, however the following revisions are recommended.

- The following statements are unclear: (b) (4)
    - The REMS Document does not explicitly state that Healthcare Providers are required to provide information on patient vaccination status to the pharmacy. In addition, the Healthcare Provider is contacted by the certified pharmacy for patient vaccination status information and this information is not provided directly to the REMS.
    - Recommend revision to these statements for clarity to the following: "Healthcare providers will be asked to provide details to the certified pharmacy on a patient's vaccination status. The certified pharmacy will assess and document a patient's vaccination status based on the information provided by the certified Healthcare Provider."

Key Risk Messages

We do not find the proposed REMS Key Risk Messages (KRM's) acceptable. The KRM's should include more detail related to specific measures taken to mitigate the risk of meningococcal infections and should be listed separately for healthcare providers and patients. Incorporate the following revisions to the KRM's into section 3.2.5 REMS Key Risk Messages in the Supporting Document.

Healthcare Providers (HCPs):

1. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors; ZILBRYSQ is a complement inhibitor.
2. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Closely monitor patients for early signs and symptoms of meningococcal infections and evaluate immediately if infection is suspected.
3. Complete or update meningococcal vaccination (for serogroups A, C, W, and Y [MenACWY], and serogroup B [MenB]) at least 2 weeks prior to administering the first dose of ZILBRYSQ,

according to current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccinations in patients receiving a complement inhibitor.

- Because of inhibition of complement activity by ZILBRYSQ and risk of infection caused by nongroupable strains of Neisseria meningitidis, vaccination does not eliminate the risk of meningococcal infections, despite development of antibodies following vaccination.
- If urgent ZILBRYSQ therapy is indicated in a patient who is not up to date with both MenACWY and MenB vaccines according to ACIP recommendations, administer meningococcal vaccine(s) as soon as possible and provide the patient with antibacterial drug prophylaxis.

4. Withhold administration of ZILBRYSQ in patients who are undergoing treatment for meningococcal infection until the infection is resolved.
5. Counsel patients using the **Patient Safety Card** and **Patient Guide**.
    - Counsel patients to carry the **Patient Safety Card** at all times during treatment and for 2 months after the last dose of ZILBRYSQ and to show the card to any healthcare provider that provides treatment.
    - Tell patients to seek immediate medical attention if they develop any of the following symptoms: headache with nausea, vomiting, stiff neck, stiff back, or fever; fever with or without a rash; sensitivity of eyes to light; confusion muscle aches with flu-like symptoms

Patients:

1. ZILBRYSQ increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections can be infections of the blood, linings of the brain, and spinal cord.
2. Meningococcal infections may become life threatening and cause death if not recognized and treated early.
3. Receive or update both meningococcal vaccines at least 2 weeks before your first dose of ZILBRYSQ or as soon as possible if you have not already had these vaccines.
4. If you have not completed vaccinations for meningococcal infections at least 2 weeks before your first ZILBRYSQ dose and ZILBRYSQ therapy must be started right away, take antibiotics as directed by your doctor.
5. Call your doctor or get emergency medical care right away if you get any signs or symptoms of a meningococcal infection. Signs and symptoms may include:
    - Headache with nausea, vomiting, stiff neck, stiff back, or fever; fever with or without a rash; sensitivity of eyes to light; confusion muscle aches with flu-like symptoms
6. Carry the **Patient Safety Card** with you at all times during treatment and for 2 months after your last dose of ZILBRYSQ. Show the card to any healthcare provider that treats you.

Key Performance Indicators

The Key Performance Indicators and associated target thresholds proposed by the Applicant are acceptable. We recommend adjusting the rationale for the KPI #1 target threshold to reflect the lower target threshold of 80%.

REMS Assessment Plan

Include in the REMS Supporting Document a revised Zilbrysq REMS Assessment Plan that addresses these comments.

Revisions to the REMS Assessment Plan are needed to inform on the goal and objectives of the proposed REMS. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in ~~strikethrough~~.

We do not agree with your proposed changes to metrics 7b and 7ei:

- For metric 7b, "The number and percentage of new patients treated with ZILBRYSQ who (b) (4) or were up to date with meningococcal vaccinations (MenACWY and MenB) as per the most current Advisory Committee on Immunization Practices (ACIP) recommendations" replace (b) (4) with "completed" to align with the revised Zilbrysq label.
- For metric 7ei, " (b) (4) meningococcal vaccines (received both MenACWY and MenB)", replace the phrase (b) (4) with "Completed" to align with the revised Zilbrysq label.

We agree with your minor edits to metrics 8bv and have one additional revision as follows:

- For metric 8bii, "Date of (b) (4)….", replace (b) (4) with "event" to clarify data that is to be reported for cases of meningococcal infection in the United States.

Resubmission Instructions

Submit a REMS amendment within 5 business days that addresses these comments.

The following materials contain revisions. If you find these acceptable, update the materials with the revisions and resubmit these materials with the next complete submission. Indicate any new changes you propose as redlined changes in your next submission. Include all formatting when submitting REMS materials in your next submission, including logos, coloring, shading, or other design features.

- REMS Document
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Guide

Your complete REMS proposal should be submitted as separate documents in the same submission, should include Word tracked changes version, a Word clean version, and a .pdf version of each of the documents and appended materials. See the chart below with a summary of required formats for document submission.

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, Clean PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, Clean PDF version
3	Prescriber Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version

4	Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version
5	Healthcare Provider Safety Brochure	Tracked MS Word, Clean MS Word, Clean PDF version
6	Patient Safety Card	Tracked MS Word, Clean MS Word, Clean PDF version
7	Patient Guide	Tracked MS Word, Clean MS Word, Clean PDF version
8	REMS Letter: Vaccination reminder to REMS certified prescribers	Tracked MS Word, Clean MS Word, Clean PDF version
9	REMS Website	Tracked MS Word, Clean MS Word, Clean PDF version
10	Compiled PDF file that **includes the REMS Document and all REMS materials** in their final, clean format	PDF Version

8. References

1. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Original Submission (Orig-1). August 31, 2022.
2. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Amendment (sequence 0007). November 14, 2022.
3. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Response to IR (sequence 0043). June 16, 2023.
4. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Response to IR and REMS Amendment (sequence 0048). July 31, 2023.
5. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Amendment (sequence 0052). August 29, 2023.
6. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Draft Prescribing Information, Agency edits as of September 1, 2023.
7. Matthews, M. Zilbrysq (zilucoplan) proposed REMS Interim Comments. NDA 216834. August 24, 2023.
8. Matthews M. Information Request - Agency Revised Labeling for Zilbrysq (zilucoplan). NDA 216834. August 24, 2023.
9. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Draft Prescribing Information, August 29, 2023.
10. Freilich E. Food and Drug Administration. Division of Neurology 1. Major amendment acknowledgement letter for zilucoplan, NDA 216834. August 30, 2023.

9. Appendix

Assessment Plan

REMS Document

Prescriber Enrollment Form

Pharmacy Enrollment Form

Healthcare Provider Safety Brochure

Patient Guide

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/s/

SARAH K HOLMAN
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CYNTHIA L LACIVITA on behalf of ANAHITA TAVAKOLI
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BARBARA A BERGQUIST
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CYNTHIA L LACIVITA
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U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Neuroscience
Division of Neurology 1

NDA#:	216834
Products:	Zilbrysq (zilucoplan), subcutaneous injection
APPLICANT:	UCB, Inc.
FROM:	Teresa Buracchio, MD
DATE:	August 28, 2023

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 consultation between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Zilbrysq (zilucoplan) to ensure that the benefits of the drug outweigh the risks of serious life-threatening or potentially fatal meningococcal infections. In reaching this determination, we considered the following:

A. Zilbrysq (zilucoplan) will be indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. The estimated number of patients in the United States with myasthenia gravis is 36,000 to 60,000. This estimate is based on information from the Myasthenia Gravis Foundation of America.[1] Generalized myasthenia gravis (i.e., not limited to ocular motor symptoms) accounts for the majority of myasthenia gravis. Approximately 74-88% of patients with gMG have AChR antibodies.[2]

B. Generalized myasthenia gravis is an autoimmune disorder of neuromuscular transmission characterized by skeletal muscle weakness. Symptoms include ocular motor symptoms of ptosis and diplopia that can interfere with normal vision, with progression to other muscle groups resulting in diffuse muscle weakness that can become life-threatening when the muscles responsible for breathing become involved. Myasthenic crisis requires intensive care and respiratory support.[3]

C. After 12 weeks of treatment with Zilbrysq (zilucoplan), adult patients with gMG had statistically significant and clinically meaningful improvement compared to patients treated with placebo in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL), which assesses the impact of generalized myasthenia gravis on daily functions, and on the Quantitative Myasthenia Gravis (QMG) total score, which assesses muscle weakness.

D. Zilbrysq (zilucoplan) will be used daily on a chronic basis in patients with generalized myasthenia gravis who are AChR antibody positive.

E. Zilbrysq (zilucoplan) is a complement inhibitor that binds to component 5 (C5) and blocks its activation. *Neisseria meningitidis* is cleared by terminal complement components, and C5 inhibition is associated with meningococcal infections.[4] Life-threatening or fatal infections may occur after treatment with C5 inhibitors. Patients may also have an increased risk of infections with other *Neisseria* infections, such as *Neisseria gonorrhoeae*. Patients may also be at increased risk for pancreatitis.

F. Zilbrysq (zilucoplan) is a new molecular entity.

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[1] https://myasthenia.org/MG-Education/MG-Quick-Facts#:~:text=The%20most%20common%20form%20of,approximately%2036%2C000%20to%2060%2C000%20cases.
[2] Howard JF. Ann. N.Y. Acad. Sci. 2018; 1412:113-128.
[3] Gilhus NE, Tzartos S. Evoli A, Palace J, Burns TM, Verschuuren JGM. Nat Rev Dis Primers 2019; 5 (30) https://doi.org/10.1038/s41572-019-0079-y
[4] Socie G, Caby-Tosi M-P, Marantz JL et al. Br J Haematol 2019; 185:297-310.

The elements of the REMS will be elements to assure safe use, including that healthcare providers who prescribe Zilbrysq (zilucoplan) are specially certified, pharmacies and healthcare settings that dispense zilucoplan are specially certified, the drug is dispensed to patients with evidence or other documentation of safe use [vaccination history including antibiotic prophylaxis will be assessed and documented by pharmacies that dispense Zilbrysq (zilucoplan)], an implementation system, and a timetable for submission of assessments of the REMS.

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/s/

TERRY HARRISON
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08/28/2023 11:52:57 AM

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	NDA
Application Number	216834
PDUFA Goal Date	August 31, 2023
Nexus TTT#	2022-1164
Reviewer Names	Sarah K. Holman, PharmD, BCPS (DRM) Anahita Tavakoli, MA (DRM) Judine Berlus, PharmD, MPH Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Team Leaders	Barbara Bergquist, PharmD (DMAMES) Jacqueline Sheppard, PharmD (DRM)
Associate Division Director for REMS Design and Strategy	Laura Zendel, PharmD, BCPS (DRM)
Review Completion Date	August 24, 2023
Subject	Interim Review of Proposed REMS
Established Name	Zilucoplan
Trade Name	Zilbrysq
Name of Applicant	UCB, Inc.
Therapeutic Class	Complement C5 inhibitor
Formulation(s)	Subcutaneous injection solution 40 mg/mL (single-use prefilled syringe)
Dosing Regimen	

Body Weight	Once Daily SubQ Dosage	Plunger Rod Color of Prefilled Syringe (PFS)
Less than 56 kg	16.6 mg	RUBINE RED
56 kg to less than 77 kg	23 mg	ORANGE
≥77 to <150 kg	32.4 mg	DARK BLUE

TABLE OF CONTENTS

1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Zilbrysq (zilucoplan), New Drug Application (NDA) 216834, submitted by UCB, Inc. (hereafter referred to as the Applicant) on August 31, 2022 and amended on November 14, 2022, June 16, 2023, and July 31, 2023.[1-4]

Zilbrysq is a complement protein 5 (C5) inhibitor proposed for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive.[5] This application is under review in the Division of Neurology 1 (DN1).

The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system (IS), and a timetable for submission of assessments to ensure the benefits of zilucoplan outweigh the risk of meningococcal infections.

This interim review provides comments on the June 16, 2023, and July 31, 2023 REMS amendments, and the August 4, 2023 information request response. In the June 16, 2023 amendment, the Applicant proposed changes to the REMS materials in response to the Agency comments sent on June 2, 2023.[6] In the July 31, 2023 amendment, the application proposed administrative changes to the REMS materials related to adverse event reporting methods, provided clarification on pharmacy processes, and proposed key risk messages for the REMS in response to an information request sent by the Agency on July 24, 2023.[7] In the August 4, 2023 information request response, the Applicant proposed revisions to the key performance indicator (KPI) and proposed a KPI target threshold in response to comments sent by the Agency on 7/28/23.[8,9]

The proposed changes to the REMS include:

- REMS Document, REMS Materials, REMS Website, and Supporting Document
  - Change to the adverse event reporting methods (b) (4)
- REMS Document
  - Updated REMS goals and objectives to focus on mitigation, occurrence, and morbidity associated with meningococcal infections and align with the public health prevention aims of primary and secondary prevention
  - Aligned the REMS Document with the REMS Document Technical Conformance Guide
  - Added section in participant requirements for wholesaler, distributor, and other entities that distribute zilucoplan
  - Revised timetable for submission of assessments
- Prescriber Enrollment Form, Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, Patient Guide, and REMS Letter: Vaccination reminder to REMS certified prescribers
  - Updated to reflect changes made to the REMS Document and to incorporate the Agency's recommended edits
- REMS Website
  - Updated to reflect changes to the REMS Document and REMS materials
- Supporting Document
  - Revised to align with changes made to the REMS Document
  - Added section on implementation system
  - Added section on key risk messages
  - Added section on key performance indicators

2. Regulatory History

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

- **06/02/2023**: Interim Comments issued to Applicant. Agency recommended revision of the REMS goal and objectives, revisions of the REMS Document to align with the REMS Document Technical Conformance Guide, addition of a section in the REMS Document for wholesaler, distributors, and other entities that distribute zilucoplan, and updates to the timetable for submission of assessments.[6]
- **06/16/2023**: Applicant submitted a REMS amendment in response to the Agency's June 2, 2023 comments.[3]
- **07/24/2023:** The Agency sent an information request to the Applicant with questions regarding pharmacy processes and key risk messages, and requesting submission of REMS materials impacted by an administrative change related to adverse event reporting.[7]
- **07/28/2023**: Interim comments issued to the Applicant by the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES). DRM contributed comments to the review related to revision of the REMS key performance indicator (KPI) and asked the Applicant to propose a KPI threshold.[8]
- **07/31/2023**: Applicant submitted a REMS amendment and response to the Agency's July 24, 2023 information request.[4]
- **08/04/2023**: Applicant submitted a communication in response to the comments sent on 07/28/2023 regarding the KPI.[9]

3. Review of Applicant's Proposed REMS

3.1. REMS Goals

The Applicant proposed to revise the primary objective (b) (4) (b) (4) The Applicant's rationale for this change was (b) (4) (b) (4)

Reviewer comments:

We agree with the proposed change to the primary objective and have other revisions to the REMS Goal and objectives to improve clarity and align with changes to labeling. The REMS Goal and objectives have been revised to the following:

(b) (4) *The goal of the Zilbrysq REMS is to mitigate the risk of serious meningococcal infection.*

(b) (4)

1) *Patients are vaccinated against meningococcal infection caused by Neisseria meningitidis serogroups A, C, W, Y (MenACWY) and serogroup B (MenB) prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed*

2) *Patients are aware of the early signs and symptoms of meningococcal infection and the need for immediate medical evaluation*
3) *Prescribers are aware of the early signs and symptoms of meningococcal infection and the need for immediate medical evaluation*

3.2. REMS Document

The Applicant incorporated the Agency's requested changes to the REMS Document including addition of risk information to Section 1: Administrative Information, addition of Section 6: Statutory Elements, addition of a section for wholesaler, distributor, and other entities that distribute zilucoplan, and removal of language regarding (b) (4)

The Applicant additionally made revisions to the REMS Document to align with the REMS Document Technical Conformance Guide[10] and to correct typographical errors.

Reviewer comments:

The changes proposed by the Applicant to align with the Technical Conformance Guide and to correct typographical errors are acceptable.

The Agency has revised the REMS Document participant requirements to align with the revisions to the label sent to the Applicant on August 24, 2023, and for consistency with the REMS Document Technical Conformance Guide. See attached redlined REMS Document for additional comments and Agency edits.

3.3. REMS Requirements

3.3.1. REMS Participant Requirements

3.3.1.1. Healthcare Provider

The Applicant proposed removal (b) (4) for the healthcare provider requirements before treatment initiation. The Applicant provided the rationale that (b) (4) does not apply to bullets 4 through 7 in the healthcare provider requirements of the REMS Document. The Applicant believes this verbiage could cause confusion (b) (4)

Reviewer comments:

The Applicant's proposed change is acceptable. In addition, the Agency provided revisions to the healthcare provider requirements in the REMS Document to align with updated labeling. See attached redlined document.

3.3.1.2. Patient

The Applicant proposed removal (b) (4) for the patient requirements before treatment initiation with similar reasoning to Section 3.2.1.1 above.

Reviewer comments:

The Applicant's proposed change is acceptable. In addition, the Agency provided revisions to the patient requirements in the REMS Document to align with updated labeling. See attached redlined document.

3.3.1.3. Pharmacy

The Applicant did not propose changes to the pharmacy requirements.

Reviewer comments:

The Agency provided revisions to the pharmacy requirements in the REMS Document to align with updated labeling. See attached redlined document.

3.3.2. REMS Applicant Requirements

3.3.2.1. Operations

The Applicant proposed the following changes in the Applicant requirements to support REMS operations.

- Removing (b) (4) in bullet 6 as an administrative change related to adverse event reporting methods.
- Addition of the following language to bullet 7: "Ensure that once a report suggestive of meningococcal infection is received, UCB, Inc. will follow up with the healthcare providers to (b) (4) obtain all required data."
- Changed the word "database" to (b) (4) in bullets 12 and 13

Reviewer comments:

We find the change related to adverse event report methods in bullet 6 acceptable. We do not agree with addition of language in bullet 7 to (b) (4) obtain required data regarding reports of meningococcal infection. We understand that there will be a process in place for the Applicant to obtain all the required data and it is understood that the Applicant may not reach all prescribers, however it is implied that the Applicant would attempt to collect this data and this qualifier is unnecessary. We also do not agree with changing "database" to (b) (4) as this does not align with the Technical Conformance Guide and the term database encompasses both a searchable database and a simple database, (b) (4)

3.3.2.2. Compliance

The Applicant proposed revising the audit timeframe for wholesalers, distributors, and other entities that distribute Zilbrysq to "within (b) (4) calendar days after their first commercial distribution of ~~Zilbrysq~~ (b) (4) and annually thereafter…". The Applicant's rationale for this change is it was unclear when audits should occur if another entity is added to the supply chain.

Reviewer comments:

This change to the audit timeframe for wholesalers, distributors, and other entities that distribute Zilbrysq as relates to the timing from the first commercial distribution is

acceptable, however the language should be further revised as follows to align with bullet 18: "Audit wholesalers, distributors, and other entities that distribute ZILBRYSQ no later than (b) (4) calendar days after their first commercial distribution of ZILBRYSQ and annually thereafter…"

3.3.3. REMS Materials

The Applicant incorporated the Agency's changes requested in Agency comments on June 2, 2023 to the Healthcare Provider Safety Brochure, Prescriber Enrollment Form, Pharmacy Enrollment Form, Patient Safety Card, Patient Guide, and REMS Letter: Vaccination reminder to REMS certified prescribers.[6] The materials were further revised by the Applicant to align with the language in the REMS Document.

The Applicant added an additional statement in the Patient Guide to describe that patients may require additional doses of meningococcal vaccines during treatment and the importance that vaccines are up to date.

Reviewer comments:

We find the changes to the Healthcare Provider Safety Brochure, Patient Guide, Patient Safety Card, Pharmacy Enrollment Form, Prescriber Enrollment Form, and REMS Vaccination Reminder Letter acceptable.

Throughout all the materials, the Applicant should change the name of the "Patient (b) (4) " to "Patient Guide."

We revised all of the REMS materials to incorporate recommendations provided by the Office of Prescription Drug Promotion (see Section 6 below for further details). We further revised all the REMS materials to incorporate changes to the draft prescribing information (PI) and Medication Guide (MG) that was sent to the Applicant by the Agency on August 24, 2023. These changes to the PI and MG were primarily in relation to the language surrounding the required meningococcal vaccines and antibacterial drug prophylaxis.

The Applicant should revise all REMS materials to incorporate changes to the labeling related to requirements for vaccination and antibacterial drug prophylaxis sent by the Agency on August 24, 2023. See the attached materials with the Agency's redlined versions of the materials for reference.

REMS Website

The Applicant did not incorporate the requested change to the REMS website to remove the (b) (4) from the top section of every page. The Applicant did incorporate the requested changes to 1) include sections for all stakeholders and actions each needed to take, a section on "What is the ZILBRYSQ REMS," and the drug indication on the landing page, 2) used the Agency's language to define a REMS, and 3) incorporated the changes made to the REMS Document and REMS materials on the REMS website.

Reviewer comments:

We do not find the proposed REMS website to be acceptable. The website should be updated to align with the most recent revisions to the REMS Document and REMS materials. Given the screenshot format of the REMS website material, the comments on the website are listed below

rather than as redlines to the document. The following additional edits are necessary to the REMS website:

- *At the top of each page, the Applicant should remove* [redacted] (b) (4)
- *The Applicant should change Patient* [redacted] (b) (4) *to "Patient Guide" throughout website*
- *The Applicant should remove* [redacted] (b) (4) *at the top of each REMS webpage*
- *On the home page (1.1)*
    - *The Applicant should remove "What is the ZILBRYSQ REMS* [redacted] (b) (4) *and replace with language below:*
        - *"What is the ZILBRYSQ REMS (Risk Evaluation and Mitigation Strategy)?"*

          A REMS is a strategy to manage known or potential risks associated with a drug and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. ZILBRYSQ has a REMS because it increases your chance of getting a meningococcal infection. The infection can quickly become life threatening or fatal if not recognized and treated early. ZILBRYSQ is only available through a restricted distribution program called the ZILBRYSQ REMS.
    - *The Applicant should update the REMS goal and objectives based on revisions to the REMS Document*
    - *The Applicant should revise the statement in the box titled "Patients" to the following:* [redacted] (b) (4) *meningococcal vaccines prior to starting ZILBRSYQ therapy.* [redacted] (b) (4) *understand the need for immediate medical attention for any signs or symptoms of meningococcal infection."*
    - *The Applicant should revise the statement in the box titled "Wholesalers and Distributors" to the following: Wholesalers, distributors, and other entities that distribute ZILBRYSQ must ensure that ZILBRYSQ is distributed only to ZILBRYSQ REMS certified pharmacies.*
    - *In the boxes titled "Prescribers" and "Pharmacies," the Applicant should revise the button to state "Start Prescriber Enrollment" and "Start Pharmacy Enrollment" to align with the title of the form and the language on the following page.*
- *On the prescriber page (1.2)*
    - *Under "2-Agree," the Applicant should separate the first bullet into two separate bullets as follows:*
        - *"Assess the patient for unresolved meningococcal infection."*
        - *"Assess the patient's meningococcal vaccine status (MenACWY and MenB)."*
    - *Under "2-Agree," the Applicant should revise the second bullet to the following: "Vaccinate the patient if needed according to the current Advisory Committee on Immunization Practices recommendations."*
- *On the prescriber certification page (1.3)*
    - *The Applicant should update the prescriber agreement with revisions to the prescriber attestations in the Prescriber Enrollment Form*
- *On the pharmacy page (1.4)*
    - *Under "4-Verify," the Applicant should revise the heading to the following: "Verify prescriber certification online:"*

- *Under "4-Verify," the Applicant should remove the word (b) (4) prior to "access to secure look-up tool for certified prescribers in the ZILBRYSQ REMS"*

- *On the pharmacy certification page (1.5)*
  - *The Applicant should update the Pharmacy Responsibilities with revisions to the pharmacy attestations in the Pharmacy Enrollment Form*
- *On the create an account page (1.7)*
  - *The Applicant should delete the word (b) (4)" from the first statement*
  - *The page indicates that only the Authorized Representative for pharmacies enrolled in the program will create a log-in and have access to the provider look-up tool. The Applicant should clarify how other pharmacy staff at the certified pharmacy will verify if prescribers are certified and if each pharmacist will be able to create a separate log-in.*
- *On the pharmacy-prescriber look-up pages (1.8 and 1.9)*
  - *The Applicant should revise the first statement to "To use the prescriber look-up tool, please provide either ZIP code, NPI number, or both prescriber last name and state, and click Search."*

3.3.4. Key Risk Messages

The Applicant proposed the following Key Risk Messages (KRM's) for the Zilbrysq REMS:

- There is an increased risk of meningococcal infections with Zilbrysq
- Patients need to be immunized against meningococcal infection prior to starting Zilbrysq
- If Zilbrysq must be started less than 2 weeks after the patient receives the first vaccine dose, a 2-week course of antibiotic prophylaxis must be taken
- It is important that patients and prescribers are able to identify early signs and symptoms of meningococcal infection and understand the need for immediate medical evaluation if infection is suspected

Reviewer comments:

The Key Risk Messages are still under review and will be addressed at a later date.

4. Supporting Document

The Applicant proposed the following changes to the Supporting Document:

- Added Section 3.2.5, REMS Key Risk Messages
- Added Section 3.2.6, REMS Key Performance Indicators. This section includes the key performance indicators (KPIs) and the target thresholds for the KPIs with a supporting rationale for the threshold
- Added Section 5, REMS Implementation System prior to the timetable for submission of assessment and Assessment Plan. Section on implementation system includes details on the REMS Website, REMS Call Center, REMS database, and noncompliance plan.

The Applicant provided details related to pharmacy processes with the REMS amendment on July 31, 2023[4] in response to an IR sent by the Agency on July 24, 2023[7]. This response included:

- The pharmacy will assess and document the patient's vaccination status and antibiotic prophylaxis prior to the first dispense of zilucoplan for a given patient. The pharmacy will not be

required to verify receipt of subsequent vaccine doses and recommended booster doses prior to subsequent dispenses but will document those doses if that information is available.

- Explanation of the process if the pharmacy is unable to document vaccination status and/or antibiotic prophylaxis: (b) (4)

Reviewer comments:

We find the addition of Sections 3.2.5 (REMS Key Risk Messages) and 3.2.6 (REMS Key Performance Indicators) to the Supporting Document acceptable. The content of Section 3.2.5 and Section 3.2.6 are addressed above in Section 3.3.4 and Section 5 below. We find the addition of Section 5 (REMS Implementation System) and its content acceptable.

We do not agree that the certified pharmacy should assess and document the patient's vaccination status and antibacterial drug prophylaxis (b) (4) *As some patients may not be up to date on the meningococcal vaccines at the time of the first dispense, the pharmacy should continue to assess and document this information if needed for up to 6 months after the first dispense to allow documentation of completion of the meningococcal vaccine series in those patients. If a patient is determined by the pharmacy to be up to date on both meningococcal vaccines (MenACWY and MenB) prior to 6 months after the first dispense of zilucoplan, then the pharmacy is not expected to continue to collect further data prior to subsequent dispenses. This revision aligns with the labeling changes communicated by the Agency on August 24, 2023.*

Given the nature of the disease of myasthenia gravis and importance of prompt therapy, we do not agree (b) (4) *The pharmacy should have a process to make an attempt to collect this information from the prescriber prior to dispensing zilucoplan, however if the information cannot be obtained, the pharmacy can dispense zilucoplan but should follow up with the prescriber to collect these data. The Applicant should include in the Supporting Document additional details such as how many times the prescriber is to be contacted and at what frequency, and in what circumstances the prescription will be dispensed with missing vaccine data to avoid delays in therapy.*

As communicated in information request responses from the Applicant on November 29, 2022[11], April 13, 2023[12], and July 31, 2023[4], details related to pharmacy processes and the distribution model should be added to the Supporting Document. These descriptions should include the following:

- *Pharmacy processes*
  - *The process by which the pharmacist verifies that a prescriber is certified*
  - *How the pharmacy will assess and document patient vaccination status and antibacterial drug prophylaxis, including which dispenses the pharmacist will contact the prescriber (first dispense for all patients; up to 6 months of dispenses for patients that vaccination status is not up to date)*
  - *Specific information about the vaccines and antibiotics that the pharmacy should collect from the prescriber and document*
  - *The process by which the vaccination status and antibacterial drug prophylaxis information will be communicated to the REMS (retroactively via audits and assessment reports)*
- *Distribution model*
  - *Plan to use a third-party logistics provider direct to certified specialty pharmacy model*

4.1. REMS Assessment Plan

The proposed Zilbrysq REMS Assessment Plan is included in the REMS Supporting Document submitted on August 31, 2022, amended on November 14, 2022, and revised on June 16, 2023, and August 4, 2023.

REMS Assessment Analyst comments:

The revised REMS Assessment Plan submitted on August 4, 2023[1], is not acceptable and needs additional revisions to inform on the goal and the objectives of the proposed REMS. Refer to Appendix for the revised REMS Assessment Plan. Comments to the Applicant can be found in Section 8 of this review. These comments include requested editorial changes, additional metrics, and revisions to existing metrics.

5. Key Performance Indicators

The Agency sent comments to the Applicant on July 28, 2023 communicating that the key performance indicator (KPI) had been revised to: % of patients who received the first dose of meningococcal vaccines (MenACWY and MenB) and (b) (4) prophylaxis if needed before (b) (4). The Applicant was asked to propose a target threshold for the KPI considering the design of the REMS (vaccination is not a hard stop for dispensing), how the data will be captured, and the national rates of compliance with other vaccine schedules. In a response to the information request on August 4, 2023[9], the Applicant proposed the following:

- Retained the KPI related to prescriber certification: Percentage (%) of Zilbrysq dispensations corresponding to prescriptions written by REMS certified HCPs
    - Proposed target threshold: (b) (4)%
    - Rationale: "Based on the robust REMS design, including verification of HCP certification before each dispense, the percentage of Zilbrysq dispensations corresponding to prescriptions written by REMS certified HCPs is anticipated to be very high."
- Revised the KPI proposed by the Agency to the following: Percentage (%) of patients dispensed Zilbrysq who received the first dose of meningococcal vaccines (MenACWY and MenB) and (b) (4) prophylaxis if needed, before (b) (4) the first (b) (4)
    - Proposed target threshold: (b) (4)%
    - Rationale: "Based on robust REMS design, including educational materials and an assessment of the patient's vaccination status including antibiotic prophylaxis, if appropriate, before first Zilbrysq dispensation, the percentage of patients dispensed Zilbyrsq who received the first dose of meningococcal vaccines (MenACWY and MenB) and antibiotic prophylaxis if needed, before the first dispensation is anticipated to be very high and notably higher than what is observed for other recommended age-appropriate vaccines in the US which show a low compliance rate based on composite measures (Centers for Disease Control and Prevention [CDC], 2023)."

[1] UCB Inc. Zilbrysq (Zilucoplan). NDA 216834. Response to Information Request. August 4, 2023. Available at: \\CDSESUB1\EVSPROD\nda216834\0049\m1\us\116-risk-management-plan\rems-supporting-document-v-2-0-zilucoplan-jun-2023-tc.docx

Reviewer comments:
We agree with the proposed revisions to the KPI metric related to vaccinations, which is an outcome indicator, however this KPI should be the primary KPI and listed as KPI #1. The KPI should be revised as follows:

- *Percentage (%) of patients dispensed Zilbrysq who received the first dose of meningococcal vaccines (MenACWY and MenB) and antibacterial drug prophylaxis if needed before the first dispense* (b) (4)

We do not agree with the proposed minimum target threshold of (b) (4) *% for this KPI. Given the REMS assessment results for related products with approved REMS in this therapeutic class, the revisions to the label sent by the Agency on August 24, 2023* (b) (4) *, the design of the REMS not requiring vaccination as a hard stop for dispensing, how the data will be collected by the pharmacy and the potential for missing data, and the national rates of compliance with other vaccine schedules, we consider 80% to be a more reasonable minimum target threshold for this KPI, and therefore recommend revision of the threshold to 80%.*

We agree with inclusion of the process indicator metric, percentage (%) of Zilbrysq dispensations corresponding to prescriptions written by REMS certified healthcare providers, as a KPI for the REMS, however this KPI should be KPI #2. The KPI should be revised as follows:

- *Percentage (%) of Zilbrysq dispenses* (b) (4) *corresponding to prescriptions written by REMS certified Healthcare Providers*

We do not agree with the proposed minimum target threshold of (b) (4) *% for the KPI. Given the pharmacy verification of prescriber certification is a closed system and our experience with closed systems in other REMS, the expected failure rate is very low and a higher threshold is achievable and more appropriate. Therefore, the KPI minimum target threshold should be revised to 99%. Refer to the 2004 IHI White Paper on "Improving the Reliability of Health Care" for further details on reliability principles.*[13]

6. Summary of Office of Prescription Drug Promotion Recommendations on REMS Materials

The Office of Prescription Drug Promotion (OPDP) was consulted on July 12, 2023 to provide feedback on the content of the *Prescriber Enrollment Form, Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Vaccination Reminder to REMS Certified Prescribers, Patient Safety Card, Patient Guide*, and Zilbrysq REMS Website. The OPDP review was completed by Roseline Boateng, Regulatory Review Officer, OPDP on August 2, 2023.

The OPDP recommendations are summarized below.

- Align the language in the REMS materials with the fully approved indication from the Prescribing Information (PI), and the final approved Medication Guide (MG).
- Revise the risk information on confusion (b) (4) in the *Healthcare Provider Safety Brochure, Patient Safety Card,* and *Patient Guide,* to be consistent with the PI.
- Fix a graphic blocking the space for the "Emergency Contact Number" in the *Patient Safety Card.*
- Throughout several REMS materials, update language to be consistent with the PI.

Reviewer comments:

We agree with OPDP's recommendations and have updated the materials accordingly. As the PI has gone through several updates since the OPDP review was finalized, all affected materials have been revised in accordance with the latest FDA-approved labeling.

7. Conclusions and Recommendations

DRM does not find the proposed REMS for Zilbrysq (zilucoplan) as submitted on August 31, 2022, and last amended on July 31, 2023, to be acceptable, as described in this review. Send the comments in Section 8 to the Applicant in an Information Request and instruct the Applicant to submit a REMS amendment within 3 business days.

8. Comments to the Applicant

We have the following comments on the proposed REMS, submitted on August 31, 2022, last amended on July 31 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

REMS Document

Revise the REMS Document to align with the revisions to the draft Prescribing Information sent by the Agency on August 24, 2023 and for consistency with the REMS Document Technical Conformance Guide. Find necessary revisions to the REMS Goal and Objectives, REMS operations, and compliance sections of the REMS Document listed below. See the attached redlined REMS Document for additional comments and Agency edits.

REMS Goal and Objectives

We agree with the proposed change to the primary objective and have other revisions to the REMS Goal and objectives to improve clarity and align with changes to labeling. Revise the REMS Goal and objectives to the following:

(b) (4) The goal of the Zilbrysq REMS is to mitigate the risk of serious meningococcal infection.

(b) (4)

1) Patients are vaccinated against meningococcal infection caused by Neisseria meningitidis serogroups A, C, W, Y (MenACWY) and serogroup B (MenB) prior to starting therapy according to the current Advisory Committee on Immunization Practices (ACIP) recommendations and receive antibacterial drug prophylaxis if needed
2) Patients are aware of the early signs and symptoms of meningococcal infection and the need for immediate medical evaluation
3) Prescribers are aware of the early signs and symptoms of meningococcal infection and the need for immediate medical evaluation

REMS Operations

In the section of the REMS Document, "To support REMS operations, UCB, Inc. must":

- We find the change related to adverse event report methods in bullet 6 acceptable.
- We do not agree with addition of language in bullet 7 to (b) (4) obtain required data regarding reports of meningococcal infection. We understand that there will be a process in place for the Applicant to obtain all the required data and it is understood that the Applicant

may not reach all prescribers, however it is implied that the Applicant would attempt to collect this data and this qualifier is unnecessary. Delete [redacted] from bullet 7.

- We do not agree with changing "database" to [redacted] in bullets 12 and 13 as this does not align with the Technical Conformance Guide and the term database encompasses both a searchable database or a simple database, [redacted]. Revert to using the term "database" in bullets 12 and 13.

Compliance

In the section of the REMS Document, "To ensure REMS participants' compliance with the REMS, UCB, Inc. must":

- In bullet 19, the change to the audit timeframe for wholesalers, distributors, and other entities that distribute Zilbrysq as relates to the timing from the first commercial distribution is acceptable. However, revise the language as follows to align with the language in bullet 18: "Audit wholesalers, distributors, and other entities that distribute ZILBRYSQ no later than [redacted] calendar days after their first commercial distribution of ZILBRYSQ and annually thereafter…"

Prescriber Enrollment Form, Pharmacy Enrollment Form, Healthcare Provider Safety Brochure, Patient Safety Card, Patient Guide, and REMS Letter: Vaccination reminder to REMS certified prescribers

We find the proposed changes to the Healthcare Provider Safety Brochure, Patient Guide, Patient Safety Card, Pharmacy Enrollment Form, Prescriber Enrollment Form, and REMS Vaccination Reminder Letter acceptable. The following edits to the above REMS materials are necessary:

- Throughout all the REMS materials, change the name of the "Patient [redacted]" to "Patient Guide."
- Revise all REMS materials to incorporate changes to the Prescribing Information and Medication Guide related to requirements for meningococcal vaccination and antibacterial drug prophylaxis sent by the Agency on August 24, 2023. See the attached materials with the Agency's redlined versions of the materials for reference.

REMS Website

We do not find the proposed REMS website to be acceptable. The website should be updated to align with the most recent revisions to the REMS Document and REMS materials. Given the screenshot format of the REMS website material, the comments on the website are listed below rather than as redlines to the document. The following additional edits are necessary to the REMS website:

- At the top of each page, remove [redacted]
- Change Patient [redacted] to **"**Patient Guide" throughout website
- Remove [redacted] at the top of each REMS webpage
- On the home page (1.1)
    - Remove "What is the ZILBRYSQ REMS [redacted] and replace with language below:
        - "What is the ZILBRYSQ REMS (Risk Evaluation and Mitigation Strategy)?"

          A REMS is a strategy to manage known or potential risks associated with a drug and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. ZILBRYSQ has a REMS because it increases your chance of getting a meningococcal infection. The infection can quickly become life threatening or

fatal if not recognized and treated early. ZILBRYSQ is only available through a restricted distribution program called the ZILBRYSQ REMS.

- Update the REMS goal and objectives based on revisions to the REMS Document
- Revise the statement in the box titled "Patients" to the following: (b) (4) meningococcal vaccines prior to starting ZILBRSYQ therapy. (b) (4) understand the need for immediate medical attention for any signs or symptoms of meningococcal infection."
- Revise the statement in the box titled "Wholesalers and Distributors" to the following: "Wholesalers, distributors, and other entities that distribute ZILBRYSQ must ensure that ZILBRYSQ is distributed only to ZILBRYSQ REMS certified pharmacies."
- In the boxes titled "Prescribers" and "Pharmacies" revise the button to state "Start Prescriber Enrollment" and "Start Pharmacy Enrollment" to align with the title of the form and the language on the following page.

- On the prescriber page (1.2)
  - Under "2-Agree," separate the first bullet into two separate bullets as follows:
    - "Assess the patient for unresolved meningococcal infection."
    - "Assess the patient's meningococcal vaccine status (MenACWY and MenB)."
  - Under "2-Agree," revise the second bullet to the following: "Vaccinate the patient if needed according to the current Advisory Committee on Immunization Practices recommendations."
- On the prescriber certification page (1.3)
  - Update the prescriber agreement with revisions to the prescriber attestations in the Prescriber Enrollment Form
- On the pharmacy page (1.4)
  - Under "4-Verify," revise the heading to the following: "Verify prescriber certification online:"
  - Under "4-Verify," remove the word (b) (4) prior to "access to secure look-up tool for certified prescribers in the ZILBRYSQ REMS"
- On the pharmacy certification page (1.5)
  - Update the Pharmacy Responsibilities with revisions to the pharmacy attestations in the Pharmacy Enrollment Form
- On the create an account page (1.7)
  - Delete the word (b) (4) from the first statement
  - The page indicates that only the Authorized Representative for pharmacies enrolled in the program will create a log-in and have access to the provider look up tool. Clarify how other pharmacy staff of the certified pharmacy will verify if prescribers are certified and if each pharmacy will be able to create a separate log-in.
- On the pharmacy-prescriber look-up pages (1.8 and 1.9)
  - Revise the first statement to "To use the prescriber look-up tool, please provide either ZIP code, NPI number, or both prescriber last name and state, and click Search."

Supporting Document

We find the addition of Sections 3.2.5 (REMS Key Risk Messages) and 3.2.6 (REMS Key Performance Indicators) to the Supporting Document acceptable. The content of the KRM's and KPI's are addressed in separate sections below. We find the addition of Section 5 (REMS Implementation System) to the Supporting Document and its content acceptable.

We do not agree that the certified pharmacy should assess and document the patient's vaccination status and antibacterial drug prophylaxis (b) (4)

As some patients may not be up to date on the meningococcal vaccines at the time of the first dispense, the pharmacy should continue to assess and document this information if needed for up to 6 months after the first dispense to allow documentation of completion of the meningococcal vaccine series in those patients. If a patient is determined by the pharmacy to be up to date on both meningococcal vaccines (MenACWY and MenB) prior to 6 months after the first dispense of zilucoplan, then the pharmacy is not expected to continue to collect further data prior to subsequent dispenses. This revision aligns with the labeling changes communicated by the Agency on August 24, 2023.

Given the nature of the disease of myasthenia gravis and importance of prompt therapy, we do not agree (b) (4) The pharmacy should have a process to make an attempt to collect this information from the prescriber prior to dispensing zilucoplan, however if the information cannot be obtained, the pharmacy can dispense zilucoplan but should follow up with the prescriber to collect these data. Include in the Supporting Document additional details such as how many times the prescriber is to be contacted and at what frequency and in what circumstances the prescription will be dispensed with missing vaccine data to avoid delays in therapy.

As communicated in information request responses from the Applicant on November 29, 2022[11], April 13, 2023, and July 31, 2023, details related to pharmacy processes and the distribution model should be added to the Supporting Document. These descriptions should include the following:

- Pharmacy processes
    - The process by which the pharmacist verifies that a prescriber is certified
    - How the pharmacy will assess and document patient vaccination status and antibacterial drug prophylaxis, including which dispenses the pharmacist will contact the prescriber (first dispense for all patients; up to 6 months of dispenses for patients that vaccination status is not up to date)
    - Specific information about the vaccines and antibiotics that the pharmacy should collect from the prescriber and document
    - The process by which the vaccination status and antibacterial drug prophylaxis information will be communicated to the REMS (retroactively via audits and assessment reports)
- Distribution model
    - Plan to use a third-party logistics provider direct to certified specialty pharmacy model

Key Performance Indicators

We agree with the proposed revisions to the key performance indicator (KPI) metric related to vaccinations, however this KPI should be the primary KPI and listed as KPI #1. The KPI should be revised as follows:

- Percentage (%) of patients dispensed Zilbrysq who received the first dose of meningococcal vaccines (MenACWY and MenB) and antibacterial drug prophylaxis if needed before the first dispense (b) (4)

We do not agree with the proposed minimum target threshold of (b) (4)% for this KPI. Given the revisions to the label sent by the Agency on August 24, 2023 (b) (4) the design of the REMS not requiring vaccination as a hard stop for dispensing, how the data will be collected by the pharmacy and the potential for missing data, and the national rates of compliance with other vaccine schedules, we consider 80% to be a more reasonable minimum target threshold for this KPI, and therefore recommend revision of the threshold to 80%.

We agree with inclusion of the metric, percentage (%) of Zilbrysq dispensations corresponding to prescriptions written by REMS certified healthcare providers, as a KPI for the REMS, however this KPI should be secondary and listed as KPI #2. The KPI should be revised as follows:

- Percentage (%) of Zilbrysq dispenses [redacted] corresponding to prescriptions written by REMS certified Healthcare Providers

We do not agree with the proposed minimum target threshold of [redacted]% for the KPI. Given the pharmacy verification of prescriber certification is a closed system and our experience with closed systems in other REMS, the expected failure rate is very low and a higher threshold is achievable and more appropriate. Therefore, the KPI minimum target threshold should be revised to 99%. Refer to the 2004 IHI White Paper on "Improving the Reliability of Health Care" for further details on reliability principles.

REMS Assessment Plan

We have the following comments on the proposed REMS Assessment Plan included in your REMS Supporting Document submitted on August 4, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final. Include in the REMS Supporting Document a revised Zilbrysq REMS Assessment Plan that addresses these comments.

Revisions to the REMS Assessment Plan are needed to inform on the goal and objectives of the proposed REMS. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in ~~strikethrough~~.

- Made minor editorial edits throughout the REMS Assessment Plan to revise [redacted] to "serogroup" and revised [redacted] to "antibacterial drug prophylaxis" to align with the updated REMS Document.
- Made minor editorial and formatting changes throughout to update the numbering and align language for metrics.
- **Metric 3: REMS Certification and Enrollment Statistics:** Added "Health Care Provider" to the metric heading to define "HCP" and made minor editorial changes.
- **Metric 4: Zilbrysq Utilization Data:** Added an additional metric to inform on the percentage of dispensed prescriptions written by certified HCPs.
- **Metric 7: Safe Use Behaviors:** Revised metrics to align with the updated REMS Document. Added a metric to inform on patients who were not initially up to date with meningococcal vaccines when starting treatment.
- **Metric 8: Summary of cases of meningococcal infections in patients receiving Zilbrysq:** Revised metric referencing the Periodic Safety Update Report to specify the corresponding reporting interval. Revised demographics for patients who had meningococcal infections. Removed metric [redacted] as this data is no longer needed to inform on the goal and objectives. Added metrics to inform on meningococcal vaccination status in US meningococcal cases. Added metric moved from metric 9. to inform on length of time between onset of symptoms and when patient presented for medical evaluation. Added a metric to report if non-US cases of meningococcal infections were associated with clinical trials.
- **Metric 9: Meningococcal Infections Rate:** Revised metric heading "Meningococcal infections [redacted] to "Meningococcal Infections Rate". Added language to report meningococcal infection rates per year and cumulatively. Moved metric to metric 8.
- **Metric 10: Knowledge**: Updated stakeholder survey metrics to assess awareness of the revised REMS objectives.

REMS Key Risk Messages

The Key Risk Messages are still under review and will be addressed at a later date.

Resubmission Instructions
Submit a REMS amendment within 3 business days that addresses these comments.

The following materials contain revisions. If you find these acceptable, update the materials with the revisions and resubmit these materials with the next complete submission. Indicate any new changes you propose as redlined changes in your next submission. Include all formatting when submitting REMS materials in your next submission, including logos, coloring, shading, or other design features.

- REMS Document
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Safety Card
- Patient Guide
- REMS Letter: Vaccination reminder to REMS certified prescribers

Your complete REMS proposal should be submitted as separate documents in the same submission, should include Word tracked changes version, a Word clean version, and a .pdf version of each of the documents and appended materials. See the chart below with a summary of required formats for document submission.

	Materials	**Required Formats**
1	REMS Document	Tracked MS Word, Clean MS Word, Clean PDF version
2	REMS Supporting Document	Tracked MS Word, Clean MS Word, Clean PDF version
3	Prescriber Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version
4	Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version
5	Healthcare Provider Safety Brochure	Tracked MS Word, Clean MS Word, Clean PDF version
6	Patient Safety Card	Tracked MS Word, Clean MS Word, Clean PDF version
7	Patient Guide	Tracked MS Word, Clean MS Word, Clean PDF version
8	REMS Letter: Vaccination reminder to REMS certified prescribers	Tracked MS Word, Clean MS Word, Clean PDF version
9	REMS Website	Tracked MS Word, Clean MS Word, Clean PDF version

10	Compiled PDF file that **includes the REMS Document and all REMS materials** in their final, clean format	PDF Version

9. References

1. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Original Submission (Orig-1). August 31, 2022.
2. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Amendment (sequence 0007). November 14, 2022.
3. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Response to IR (sequence 0043). June 16, 2023.
4. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Response to IR and REMS Amendment (sequence 0048). July 31, 2023.
5. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Draft Prescribing Information, Agency edits as of August 3, 2023.
6. Matthews, M. Zilbrysq (zilucoplan) proposed REMS Interim Comments. NDA 216834. June 2, 2023.
7. Matthews M. Information Request for Zilbrysq (zilucoplan) regarding proposed REMS. NDA 216834. July 24, 2023.
8. Matthews, M. Zilbrysq (zilucoplan) Interim Comments for the Proposed New REMS Assessment Plan. NDA 216834. July 28, 2023.
9. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Response to IR (sequence 0049). August 4, 2023.
10. Food and Drug Administration. Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research. Guidance Document. REMS Document Technical Conformance Guide. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rems-document-technical-conformance-guide. Published January 04, 2023. Accessed February 22, 2023.
11. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Response to IR (sequence 0008). November 29, 2022.
12. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Response to IR (sequence 0030). April 13, 2023.
13. Nolan T, Resar R, Haraden C, Griffin FA. Improving the Reliability of Health Care. IHI Innovation Series white paper. Boston: Institute for Healthcare Improvement; 2004.

10. Appendix

Assessment Plan

REMS Document

Prescriber Enrollment Form

Pharmacy Enrollment Form

Healthcare Provider Safety Brochure

Patient Safety Card

Patient Guide

REMS Letter: Vaccination reminder to REMS certified prescribers

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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/

SARAH K HOLMAN
08/24/2023 01:44:51 PM

ANAHITA TAVAKOLI
08/24/2023 01:46:37 PM

JUDINE J BERLUS
08/24/2023 01:54:26 PM

JO H WYETH on behalf of BARBARA A BERGQUIST
08/24/2023 02:18:40 PM

JACQUELINE E SHEPPARD
08/24/2023 02:50:25 PM

LAURA A ZENDEL
08/24/2023 03:18:57 PM

Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRM only and should not be used to provide comments to the sponsor.

To: Anahita Tavakoli, Health Communications Analyst
Division of Risk Management (DRM)
Office of Surveillance and Epidemiology (OSE)

From: Roseline Boateng, Regulatory Review Officer, OPDP

CC: Kathleen Klemm, Deputy Division Director, OPDP
Emily Dvorsky, Team Leader, OPDP
Aline Moukhtara, Team Leader, OPDP
Michael Matthews, Safety Regulatory Project Manager, OSE
Jacqueline Sheppard, Team Leader, DRM
Katie (Sarah) Holman, Risk Management Analyst, DRM
Jina Kwak, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: August 2, 2023

Re: NDA 216834
ZILBRYSQ (zilucoplan) injection, for subcutaneous use
Comments on Draft Risk Evaluation and Mitigation Strategies (REMS) Materials

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Materials Reviewed

OPDP has reviewed the following proposed REMS materials for ZILBRYSQ (zilucoplan) injection, for subcutaneous use (Zilbrysq):

- Healthcare Provider (HCP) REMS Materials:
  - Prescriber Enrollment Form
  - Pharmacy Enrollment Form
  - Healthcare Provider Safety Brochure
  - Vaccination Reminder to REMS Certified Prescribers

- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Safety Card
  - Patient (b) (4)

- Zilbrysq REMS Website

The version of the draft REMS materials used in this review were sent from DRM (Anahita Tavakoli) via email on July 12, 2023. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Zilbrysq.

General Comment

Please remind UCB, Inc. that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.ZILBRYSQREMS.com and toll-free number 1-877-414-8353. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind UCB, Inc. that the REMS specific website should not be the sole source of approved REMS materials.

Comments are provided using the draft product labeling (PI, Medication Guide and Instructions For Use) for Zilbrysq sent via email on July 21, 2023.

OPDP notes that the current draft Zilbrysq PI, Medication Guide (MG) and Instructions For Use (IFU) are still being reviewed by DN1. Therefore, we recommend that the REMS materials be revised, as appropriate, to reflect all changes in the final approved label for Zilbrysq.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see "Specific Comments" below):

- Healthcare Provider (HCP) REMS Materials:
  - Prescriber Enrollment Form
  - Pharmacy Enrollment Form
  - Healthcare Provider Safety Brochure
  - Vaccination Reminder to REMS Certified Prescribers

- Direct-to-Consumer (Patient) REMS Materials:
  - Patient Safety Card
  - Patient (b) (4)

- Zilbrysq REMS Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising them in the REMS piece:

- **Prescriber Enrollment Form**

  - Page one of the form includes an "Instructions" section that lists steps to take, including documents to review and how to submit the form.

    - **Risk**
      - This presentation may minimize the REMS risk associated with Zilbrysq by not disclosing that Zilbrysq is only available through a restricted distribution program that is part of the REMS program, due to the risk of meningococcal infections.
      - OPDP recommends adding this risk information to be consistent with competitors (Soliris and Ultomiris).

  - Page two of the form states, (b) (4)

    - **Risk**
      - This presentation may minimize the REMS risk associated with Zilbrysq (b) (4)

- OPDP recommends revising the risk information in the REMS piece to be consistent with the draft PI.

- **Pharmacy Enrollment Form**

  - Page one of the form includes an “Instructions” section that lists steps to take, including documents to review and how to submit the form.

    - **Risk**
      - This presentation may minimize the REMS risk associated with Zilbrysq by not disclosing that Zilbrysq is only available through a restricted distribution program that is part of the REMS program, due to the risk of meningococcal infections.
      - OPDP recommends adding this risk information.

- **Healthcare Provider Safety Brochure**

  - Page four of the brochure includes the statement, “Educate patients to recognize the signs and symptoms of meningococcal infections, and instruct patients to seek immediate medical (b) (4) Signs and symptoms (b) (4) …**Confusion** (b) (4) (emphasis added).

    - **Risk**
      - We are concerned that this presentation may be misleading as it minimizes the REMS risk of the drug by implying that “confusion” and (b) (4) might be similar.
      - OPDP recommends revising the risk information in the REMS piece to be consistent with section 17 PATIENT COUNSELING INFORMATION of the draft PI (b) (4)

- **Patient Safety Card**

  - The patient safety card includes the following statement, “Call your healthcare provider or seek emergency care immediately if you have any of these signs and symptoms of meningococcal infection: …**Confusion** (b) (4) (emphasis added).

    - **Risk**
      - We are concerned that this presentation may be misleading as it minimizes the REMS risk of the drug by implying that “confusion” and (b) (4) might be similar.
      - OPDP recommends revising the risk information in the REMS piece to be consistent with the draft MG (b) (4)

- The patient safety card includes the following spaces for contacts, Patient Name, Prescriber Name, Prescriber Phone Number and Emergency Contact Number.

  - **General comment**
    - We are concerned that the graphics block the space for the "Emergency Contact Number." Please consider editing so that all important information is visible.

- The patient safety card states, (b) (4)

  - **Risk**
    - This presentation may minimize the REMS risk associated with Zilbrysq (b) (4)
    - OPDP recommends revising the risk information in the REMS piece to be consistent with the draft PI.

- **Patient** (b) (4)

  - Page one states, "ZILBRYSQ (zilucoplan) is a prescription medicine that is used to treat adults with generalized myasthenia gravis (gMG)."

    - **Indication/Use**
      - This claim is an inadequate communication of the indication. We are concerned that this statement is broadening the patient population and leaving out material information related to the indication.
      - Per the "What is ZILBRYSQ" section of the draft MG, "ZILBRYSQ is a prescription medicine used to treat adults with a disease called generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive."
      - We recommend that the patient (b) (4) is revised to include the full approved indication.

  - Page one of the patient (b) (4) states, "Call your healthcare provider or seek emergency care right away if you have any signs or symptoms of meningococcal infection: …**Confusion** (b) (4)**"** (emphasis added).

- **Risk**
  - We are concerned that this presentation may be misleading as it minimizes the REMS risk of the drug by implying that "confusion" and (b) (4) might be similar.
  - OPDP recommends revising the risk information in the REMS piece to be consistent with the draft MG (b) (4)

- **Zilbrysq REMS Website**

  - Page six of the website states, (b) (4)

    - **Risk**
      - This presentation may minimize the REMS risk associated with Zilbrysq (b) (4)
      - OPDP recommends revising the risk information in the REMS piece to be consistent with the draft PI.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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

*****This document may contain information that cannot be released to the public*****

Application Type	NDA
Application Number	216834
Submission Type/Number	Original-1/0001
Submission Date	August 31, 2022 (sequence 0001), amended on November 14, 2022(sequence 0007) and June 16, 2023 (sequence 0043)
Reviewers	Judine Berlus, PharmD, MPH (DMAMES) Sarah K. Holman, PharmD, BCPS Division of Risk Management (DRM)
Team Lead	Barbara Bergquist, PharmD (DMAMES)
Review Completion Date	July 27, 2023
Subject	Interim Comments for the Zilbrysq (Zilucoplan) Risk Evaluation and Mitigation Strategies (REMS) Assessment Plan for the Proposed New REMS
Established Name	Zilucoplan
Proprietary Name	Zilbrysq (conditionally acceptable)
Applicant	UCB, Inc.
Therapeutic Class	Complement C5 inhibitor
Formulation	Subcutaneous injection solution 40 mg/mL (single-use prefilled syringe)
Nexus REMS TTT#	2022-2282

1. Introduction

This review provides findings from our evaluation of the proposed risk evaluation and mitigation strategy (REMS) Assessment Plan for Zilbrysq (zilucoplan) included in the REMS Supporting Document (SD) submitted on August 31, 2022, and amended on November 14, 2022 and June 16, 2023.

The Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) initiated this review in response to a consult request by the Division of Risk Management (DRM) to provide input on the quantitative and qualitative metrics that will be used to assess if the REMS is meeting its stated goal and objectives.

The Applicant submitted a New Drug Application (NDA 216834) for Zilbrysq (zilucoplan) with the proposed indication for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive[a]. This application is under review in the Division of Neurology 1 (DN1).

2. REMS Goals and Statutory Elements

2.1. REMS Goals

The proposed goal of the REMS in the REMS Document submitted on June 16, 2023[b], is to mitigate the (b) (4) meningococcal infections.

1. Patients are (b) (4) against meningococcal infection prior to starting therapy according to the Advisory Committee on Immunization Practices recommendations and receive (b) (4) prophylaxis if needed.
2. Patients are (b) (4) early signs and symptoms of meningococcal infection and the need for immediate medical evaluation.
3. Prescribers are (b) (4) early signs and symptoms of meningococcal infection and the need for immediate medical evaluation

Reviewer's comment:
The proposed goal and objectives of the Zilbrysq REMS are currently under review by the Division of Risk Management (DRM). Details on the goals will be included in a forthcoming review in conjunction with the REMS Document.

2.2. REMS Statutory Elements

The REMS consists of the following elements:

1. Elements to Assure Safe Use (ETASU)
    a. Health care providers who prescribe Zilbrysq are specially certified
    b. Pharmacies that dispense Zilbrysq are specially certified

[a] UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Original Submission (Orig-1). August 31, 2022. Available at: \\CDSESUB1\EVSPROD\nda216834\0001\m1\us\114-labeling\draft\labeling\cir-202207-sub.pdf
[b] Applicant's June 16, 2023, response to the Agency's June 2, 2023, Information Request. Available at: \\CDSESUB1\EVSPROD\nda216834\0043\m1\us\116-risk-management-plan\rems-report-body-tc.docx

c. Zilbrysq is dispensed to patients with evidence or other documentation of safe-use conditions

2. Implementation System
   The Zilbrysq REMS has an implementation system to support the elements to assure safe use. The implementation system is outlined in the REMS Document and includes processes to ensure that the REMS is functioning as intended.

2.3. Timetable for Submission of Assessments

The REMS Document submitted on June 16, 2023, proposed a timetable for submission of assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS.

Reviewer's comment:
The Applicant initially proposed submission of REMS Assessments at 6 months, (b) (4) thereafter from the date of initial approval of the REMS. Comments were sent to the Applicant on June 2, 2023[c], informing them that the proposed REMS Timetable for Submission of Assessments was not acceptable. We recommended revising the timetable to submit assessments at 6 months, 12 months, and annually thereafter, as the proposed timetable will not provide adequate data to determine if the REMS is meeting its goal and objectives and operating as intended. The Agency finds the most recent Timetable for Submission of Assessments, submitted in the June 16, 2023, REMS Document acceptable.

3. Review of the Key Performance Indicator and the REMS Assessment Plan

3.1 Key Performance Indicator

The proposed REMS assessment plan submitted by the Applicant on August 31, 2022, and amended on November 14, 2022 and June 16, 2023, included a proposed Key Performance Indicator (KPI) of enrollment of prescribers of Zilbrysq. The proposed target for this KPI is that (b) (4)% of Zilbrysq prescriptions dispensed will be written by enrolled prescribers during each REMS assessment period.

Risk Management Analyst comments:
We do not agree with the Applicant's proposed KPI related to prescriber enrollment/certification. Prescriber enrollment/certification does not indicate whether the REMS is achieving its overall goal and objectives. The KPI requires revision to align with the primary objective of the REMS, "Patients are (b) (4) against meningococcal infection prior to starting therapy according to the Advisory Committee on Immunization Practice recommendations and receive (b) (4) prophylaxis if needed."

DRM, DMAMES, and DN1 discussed and revised the KPI to make it more specific and in line with the primary objective of the REMS. Given our experience with assessment for related products with approved REMS in this therapeutic class, the Agency's thinking has evolved surrounding REMS goals, objectives, and assessment. Therefore, the KPI has been revised to the following:

[c] M Matthews. Information Request. June 2, 2023. Available at: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806d1b77

- *KPI Metric: % of patients who received the first dose of meningococcal vaccines (MenACWY and MenB) and* (b) (4) *prophylaxis if needed before* (b) (4)

The Applicant should add a new section to the Supporting Document identifying KPIs that better relate to the objectives of the REMS, the associated target thresholds, and a supporting rationale for the thresholds. The reference to the KPI will be removed from the Assessment Plan.

The review team is still discussing an appropriate KPI target threshold. This DRM reviewer considers these factors relevant to determining the minimum target threshold for the KPI: REMS assessment results for related products with approved REMS in this therapeutic class, design of the REMS (vaccination is not a hard stop for dispensing), how the data will be captured, and the national rates of compliance with other vaccine schedules.

The Applicant should propose a target threshold for the KPI considering these factors and include a rationale and any data that supports the target threshold.

3.2 REMS Assessment Plan

The proposed Zilbrysq REMS Assessment Plan is included in the REMS Supporting Document submitted on August 31, 2022, and amended on November 14, 2022 and June 16, 2023. The proposed REMS Assessment Plan includes metrics on Program Outreach and Communication, Program Implementation and Operations, Knowledge, Safe Use Behaviors and Health Outcomes. The proposed metrics are necessary to evaluate if the REMS is operating as intended and meeting its goal of mitigating the occurrence and morbidity associated with meningococcal infections.

Reviewer's Comments:
The Applicant's proposed Assessment Plan included in the Supporting Document, submitted on August 31, 2022 and amended on November 14, 2022 and June 16, 2023, needs additional revisions to inform on the goal and objectives and to ensure that the REMS is functioning as intended. (b) (4)

Additional metrics related to Utilization Data and Safe Use behaviors are necessary to inform on whether Zilbrysq is being shipped and dispensed in accordance to the REMS and if patients are being immunized per ACIP guidelines or given prophylactic antibiotics to minimize meningococcal infections. The proposed Assessment Plan will also be revised to include data on the two previous reporting periods to assess data trends over time

In Section 5 below, Comments to the Applicant, we provide comments regarding the proposed KPI and REMS Assessment Plan submitted on June 16, 2023. These comments include requested editorial changes, additional metrics, and revisions to existing metrics.

4. Conclusions and Recommendations

The proposed Key Performance Indicator and the REMS Assessment Plan, as included in the June 16, 2023, REMS Supporting Document, needs revisions. We recommend sending the comments in **Section 5** and the revised Assessment Plan to the Applicant.

5. Comments For The Applicant

We have the following comments on the proposed Key Performance Indicator and REMS Assessment Plan included in your REMS Supporting Document submitted on August 31, 2022, and amended on November 14, 2022, and June 16, 2023. Review of the REMS proposal is ongoing; these comments should not be considered final.

Key Performance Indicator

We do not agree with your proposed Key Performance Indicator (KPI) related to prescriber enrollment/certification. Prescriber enrollment/certification does not indicate whether the REMS is achieving its overall goal to prevent meningococcal infections to the extent possible through the immunization of patients and if needed antibiotic prophylaxis. The KPI requires revision to align with the primary objective of the REMS.

Revise the KPI to the following:

- % of patients who received the first dose of meningococcal vaccines (MenACWY and MenB) and (b) (4) prophylaxis if needed before (b) (4)

The reference to the KPI should not be included in the Assessment Plan. Include a description of the KPI and target thresholds in a separate section in the REMS Supporting Document along with a supporting rationale.

Propose a target threshold for the KPI considering the design of the REMS, how the data will be captured, and national rates of compliance with other vaccine schedules.

REMS Assessment Plan

The Agency requires revision to the REMS Assessment Plan. The changes are summarized below, and a tracked changed version is attached with additions underlined and deletions in strikethrough.

- Revised the metrics for the following assessment plan categories; Program Outreach and Communication, Program Implementation and Operations, Safe Use Behaviors, and Health Outcomes and/or Surrogates of Health Outcomes metrics to be reported for the two previous, current and cumulative reporting periods, where applicable, unless otherwise noted.
- Made minor editorial grammatical and formatting changes (e.g., circular bullets changed to roman numeral bullets for ease of reference when providing feedback) throughout the Assessment Plan to improve clarity.
- **Metric 1: REMS Communication activities**: Removed metrics 1.d-e (b) (4) was not included in the proposed REMS and data from those metrics are not needed. Added an additional metric, "The number and percentage of annual Vaccination REMS Reminder Letters sent via fax and email" to inform on communication to Heath Care Providers (HCPs).
- **Metric 2: REMS implementation**: Revised timeline for data to be submitted with the first REMS Assessment only, and not with each reporting period. Moved proposed metric 2a. to 2f. Added metric, to inform on the date(s) distributors/wholesalers or entities able to distribute Zilbrysq were authorized in the REMS.

- **Metric 3: REMS Certification and Enrollment Statistics:** Removed the key performance indicator from this section. Additional metrics were added for wholesaler/distributors to inform on the total number and identity of each wholesaler/distributor and other entities that distribute Zilbrysq, and those that were active.
- **Metric 4: Zilbrysq Utilization Data**: Added metrics to inform on the number of shipments of Zilbrysq from distributors/wholesalers and whether the prescriptions dispensed were new prescriptions or refills. Additional metrics added to inform on the number of unique patients who received Zilbrysq, and the number of prescriptions not dispensed, to inform on whether the Zilbrysq is being prescribed and dispensed in accordance to the REMS and to assess potential REMS related access or burden issues.
- **Metric 5: REMS Compliance**: Added metrics to inform on the number of pharmacies that were decertified and the reasons for decertification from the REMS. Revised audit metrics to include the number of audits expected for each stakeholder and additional information on authorized representatives, to inform on pharmacy compliance.
- **Metric 6: REMS Infrastructure and Performance:** Revised metric 6bi. to add reason for the contacts to the REMS Coordinating Center to inform on potential REMS related issues.
- **Metric 7: Knowledge:** Revised timeline for knowledge surveys to be submitted beginning with the 1-year assessment report and annually thereafter, as surveys are needed to evaluate if the REMS is meeting its desired goal and objectives of educating health care providers and patients. Removed (b) (4) , this language is to be moved to the Supporting Document. Added "patients", to inform on understanding of key risk messages for both HCPs and patients.
- **Metric 8: Safe Use Behaviors**: Added metrics to inform on dates of vaccine administration, timing of vaccination, vaccination dosing and whether the patient was vaccinated as per Advisory Committee on Immunization Practices (ACIP) recommendations. Also added metrics to inform on the number of patients that were not immunized or given antibiotic prophylaxis prior to initiating treatment with Zilbrysq. (b) (4)
- **Metric 9: Health Outcomes and/or Surrogated of Health Outcomes:** Added metrics to inform on clinical outcomes for cases of meningococcal infections in the United States and whether the Patient Safety Card was presented when the patient was seeking treatment.
- **Metric 10: Meningococcal infections** (b) (4) Removed "rate" from the proposed metric heading "Meningococcal infections (b) (4) rate" and added a metric (b) (4)
- **Metric 11: Overall Assessment of REMS Effectiveness:** Added the heading "Overall Assessment of REMS Effectiveness" and the requirement for assessments under section 505-1(g)(3).

Resubmission Instructions

Submit a response no later than **5 business days** that addresses these comments. Your response should include submission of your updated REMS Assessment Plan in your Supporting Document. Include both a clean version (MS Word and PDF) and a tracked changes (MS Word and PDF) version.

(b) (4)

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SARAH K HOLMAN
07/27/2023 06:48:39 AM

BARBARA A BERGQUIST
07/27/2023 07:45:46 AM

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	NDA
Application Number	216834
PDUFA Goal Date	August 31, 2023
OSE RCM #	2022-1164
Reviewer Names	Sarah K. Holman, PharmD, BCPS (DRM) Anahita Tavakoli, MA (DRM) Judine Berlus, PharmD, MPH Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)
Team Leaders	Barbara Bergquist, PharmD (DMAMES) Jacqueline Sheppard, PharmD (DRM)
Review Completion Date	June 2, 2023
Subject	Evaluation of Need for a REMS
Established Name	Zilucoplan
Trade Name	Zilbrysq
Name of Applicant	UCB, Inc.
Therapeutic Class	Complement C5 inhibitor
Formulation(s)	Subcutaneous injection solution 40 mg/mL (single-use prefilled syringe)
Dosing Regimen	0.3 mg/kg subcutaneously once daily

Body weight of patient	Dose	Prefilled Syringe (PFS)
(b) (4) <56 kg	16.6 mg	1 RUBINE RED PFS
≥56 to <77 kg	23 mg	1 ORANGE PFS
≥77 to <150 kg	32.4 mg	1 DARK BLUE PFS

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zilbrysq (zilucoplan) is necessary to ensure the benefits outweigh its risks. UCB, Inc. submitted a New Drug Application (NDA) 216834 for zilucoplan with the proposed indication for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive. The risks associated with zilucoplan include serious meningococcal infections. The applicant's proposed REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments to ensure the benefits of zilucoplan outweigh the risks of meningococcal infections.

DRM has determined that a REMS is needed to ensure the benefits of zilucoplan outweigh its risks. DRM does not find the proposed REMS submitted on August 31, 2022, and last amended on November 14, 2022, to be acceptable, as described in this review.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Zilbrysq (zilucoplan) is necessary to ensure the benefits outweigh its risks. UCB, Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 216834 for zilucoplan with the proposed indication for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive.[1] This application is under review in the Division of Neurology 1 (DN1). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system (IS), and a timetable for submission of assessments to ensure the benefits of zilucoplan outweigh the risk of meningococcal infections.

2. Background

2.1. Product Information

Zilbrysq (zilucoplan), a new molecular entity[a], is a complement protein 5 (C5) inhibitor. Through inhibition of C5, zilucoplan prevents downstream activation of the classical complement pathway which has been inappropriately activated in generalized myasthenia gravis patients. Zilucoplan inhibits the effects of C5 through two mechanisms: 1) binds to C5 to prevent its cleavage to C5a and C5b, and 2) binds to C5b to prevent binding to C6. Zilucoplan is proposed for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive.[2]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

Zilucoplan is proposed for chronic use[b] and will be supplied as a 40 mg/mL subcutaneous injection solution single-use prefilled syringe. The proposed dosing of zilucoplan is weight-based (16.6 mg, 23 mg, or 32.4 mg) administered via subcutaneous injection once daily. Zilucoplan is likely to be self-administered in the outpatient setting. Zilucoplan received orphan drug designation in June 2019 for the treatment of generalized myasthenia gravis. Zilucoplan is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216834 relevant to this review:

- **09/01/2017**: IND 134340 submitted for zilucoplan for treatment of generalized myasthenia gravis.
- **06/26/2019**: Orphan Drug Designation granted for treatment of generalized myasthenia gravis.
- **05/03/2022**: Applicant informed via pre-NDA Type B meeting preliminary comments for IND 134340 that if the Applicant plans to submit a REMS proposal with their NDA, it should include the rationale for the proposed REMS elements and the Empaveli REMS might serve as a model for how the proposed REMS could be structured.[3]
- **08/31/2022**: NDA 216834 submission for the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive received.[1]
- **11/02/2022**: The Agency sent an information request to the Applicant requesting revision of the format of the REMS Document and Microsoft Word versions of all materials.[4]
- **11/14/2022**: Applicant submitted a REMS amendment including requested format changes to the REMS materials and REMS document.[5]
- **11/18/2022**: The Agency sent an information request to the Applicant with questions regarding the proposed REMS in reference to the vaccination reminder letters for prescribers, wholesaler-distributor requirements, and the REMS coordinating center.[6]
- **11/29/2022**: Applicant submitted a communication in response to the information request sent on 11/18/2022 regarding the proposed REMS.[7]
- **02/16/2023**: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant a REMS for zilucoplan (NDA 216834) is necessary to ensure that the benefits of the drug outweigh the risks of meningococcal infections, a review of the proposed REMS is ongoing, and further information will be communicated at a later date.[8]

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- **04/05/2023:** The Agency sent an information request to the Applicant with questions regarding the authorization process for pharmacies to verify prescriber enrollment in the REMS prior to prescription dispensing.[9]
- **04/13/2023:** Applicant submitted a communication in response to the information request sent on 04/05/2023 regarding the pharmacy authorization process.[10]

3. Risk Management Activities Proposed by the Applicant

3.1. Review of Applicant's Proposed REMS

To mitigate the risk of meningococcal infections, the Applicant's initial submission on August 31, 2022, included prescribing information that contained a boxed warning, a Medication Guide as part of labeling, and a REMS. The REMS is comprised of a REMS Document, REMS materials, and REMS Supporting Document. The proposed REMS consists of ETASU that includes: prescriber certification (A), pharmacy certification (B), and documentation of safe use conditions (D), an IS, and a timetable for submission of assessments of the REMS.

3.1.1. REMS Goals

The Applicant proposed the following:

The goal of the REMS is to mitigate the (b) (4) meningococcal infections (b) (4)

(b) (4)

Reviewer's Comments: *We do not find the proposed REMS goals acceptable.* (b) (4) *However, the Agency's thinking continues to evolve regarding the development of REMS goals and objectives. When determining the goals and objectives for the REMS, we evaluated how zilucoplan will move through the drug use process, potential care gaps, and how the REMS will align with the primary public health goal which is to prevent meningococcal infections to the extent possible through the immunization of patients and if needed antibiotic prophylaxis. Another public health goal is identification of early signs and symptoms of meningococcal infection and the need for medical evaluation to mitigate the morbidity of infection should infection occur. We disagree with the Applicant's proposed goal* (b) (4) *and not the overall goal of the REMS. DRM revised the overall goal to focus on mitigation of occurrence and morbidity associated with meningococcal infections. The REMS objectives were revised to align with the public health prevention aims (primary and secondary prevention) and to allow an objective assessment of the REMS.*

We have revised the REMS goal and objectives to the following:

- *The goal of the ZILBRYSQ Risk Evaluation and Mitigation Strategy (REMS) is to mitigate the* (b) (4) *meningococcal infections.*
- (b) (4)
  - *Patients are* (b) (4) *against meningococcal infection prior to starting therapy according to the Advisory Committee on Immunization Practice recommendations*
  - *Patients are* (b) (4) *early signs and symptoms of meningococcal infection and the need for immediate medical evaluation*
  - *Prescribers are* (b) (4) *early signs and symptoms of meningococcal infection and the need for immediate medical evaluation*

3.1.2. REMS Requirements

The Applicant proposed the following ETASU as part of the REMS requirements: prescriber certification, pharmacy certification, and documentation of safe use conditions.

1. Prescriber certification (ETASU A)

To become certified to prescribe:

a) Review the (b) (4) Prescribing Information.
b) Review the following: Healthcare Provider Safety Brochure, Patient (b) (4), and Patient Safety Card.
c) Enroll (b) (4) by completing the Prescriber Enrollment Form and submitting (b) (4) to the REMS (b) (4)

Before treatment initiation

a) Counsel the patient (b) (4) using the Patient Safety Card and Patient (b) (4) Provide a copy of the materials to the patient.
b) Assess the patient's (b) (4) vaccination status and (b) (4) needed according to the current recommendations (b) (4) Advisory Committee on Immunization Practices on meningococcal vaccination.
c) Provide the patient with a prescription for (b) (4) prophylaxis (b) (4) (b) (4)

During treatment

a) Assess the patient for signs and symptoms of meningococcal infection and evaluation immediately, if infection is suspected.
b) (b) (4)
c) (b) (4) patients (b) (4) according to the current recommendations from the Advisory Committee on Immunization Practices on meningococcal vaccination.

At all times

a) Report [redacted] of meningococcal infection to UCB, Inc.

2. Pharmacy certification (ETASU B) and documentation of safe use conditions (ETASU D)

The Applicant plans to limit zilucoplan to a limited number of pharmacies and a third-party logistic provider for distribution.

To become certified to dispense

a) Designate an Authorized Representative to carry out the certification process and oversee implementation and compliance with the REMS [redacted] on behalf of the pharmacy.
b) Have the Authorized Representative review the Healthcare Provider Safety Brochure.
c) Have the Authorized Representative enroll in the REMS by completing the Pharmacy Enrollment Form and submitting [redacted] to the REMS [redacted]
d) Train all relevant staff involved in dispensing zilucoplan using the Healthcare Provider Safety Brochure.
e) Establish processes and procedures to contact the prescriber to assess the patient's vaccination status including [redacted] prophylaxis, if [redacted], and document the findings.

Before dispensing

a) [redacted] verify [redacted] the prescriber is certified.
b) Assess the patient's vaccination status including [redacted] prophylaxis, [redacted] by contacting the prescriber and document the findings through the processes and procedures established as a requirement of the REMS [redacted]

To maintain certification to dispense

a) If the Authorized Representative changes, have the new Authorized Representative enroll in the REMS by completing the Pharmacy Enrollment Form and submitting [redacted] to the REMS [redacted]

At all times

a) Report [redacted] of meningococcal infection to UCB, Inc.
b) Maintain records of staff's completion of REMS training.
c) Maintain records that all processes and procedures are in place and are being followed.
d) Comply with audits carried out by UCB, Inc. or a third party acting on behalf of UCB, Inc. to ensure that all processes and procedures are in place and being followed.

3. Patients who are prescribed zilucoplan

Before treatment initiation

a) Receive counseling from the prescriber using the Patient Safety Card and Patient [redacted]
b) Get meningococcal vaccines as directed by your [redacted]
c) Take antibiotic [redacted] as directed by your [redacted] if you have to start zilucoplan right away.

During treatment

a) Get meningococcal vaccines as directed by your [redacted] (b) (4)

At all times

a) Inform the prescriber or get emergency medical care right away if [redacted] (b) (4)
b) Have the Patient Safety Card with you

Reviewer's Comments:

We agree with the Applicant's proposal to require prescriber certification (ETASU A), pharmacy certification (B), and documentation of safe use conditions (ETASU D). See the attached REMS Document appended to this review for additional revisions.

- *Revision to align with the REMS Document Technical Conformance Guide[11] including addition of risk information to Section 1: Administrative Information and addition of Section 6: Statutory Elements.*
- *Addition of a section to participant requirements for wholesaler, distributor, and other entities that distribute zilucoplan. Added language "and other entities that distribute ZILBRYSQ" when referencing wholesalers and distributors as UCB plans to use a third-party logistics provider (3PL) distribution model.*
- *Removal of language regarding* [redacted] (b) (4)

3.1.3. Implementation System

Elements of an implementation system are listed in the REMS Document which include:

- REMS Website
- REMS Call Center
- Validated, secure database
- Establish plans to detect and address noncompliance with REMS requirements
- Take reasonable steps to improve implementation of and compliance with the requirements of the REMS

Reviewer's Comments*: The Applicant proposed appropriate elements of an implementation system in the REMS Document; however, the implementation system was not adequately described in the Supporting Document. The Applicant should incorporate a section describing the implementation system for the REMS into the Supporting Document prior to the timetable for submission of assessments and Assessment Plan.*

3.1.4. Timetable for Submission of Assessments

The Applicant proposed to submit REMS Assessments at 6 months, [redacted] (b) (4) thereafter from the date of initial approval of the REMS.

Reviewer's Comments: *The Division of Mitigation and Medication Error Surveillance (DMAMES) does not agree with the proposed timetable for submission of assessments. To determine whether the goals and objectives of the REMS are being met and that the REMS is functioning as intended, REMS assessments are to be submitted at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS.*

3.1.5. REMS Materials & Key Risk Messages

Key Risk Messages

The Applicant did not propose any Key Risk Messages.

Reviewer's Comments*: The key risk messages by DRM are still under discussion and development.*

REMS Materials

The Applicant included the following materials as part of the original submission of the REMS:

- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Safety Card
- Patient (b) (4)
- REMS Letter: Vaccination reminder to REMS certified prescribers
- REMS Website

Reviewer's Comments*:*

Prescriber Enrollment Form and Pharmacy Enrollment Form

All attestations which are included in the Prescriber and Pharmacy Enrollment Forms should reflect the language in the REMS Document and REMS requirements. The prescriber and pharmacy attestations were revised to align with the changes made to the REMS Document. See attached revised Prescriber Enrollment Form and Pharmacy Enrollment Form appended to this review.

Healthcare Provider Safety Brochure

We have made edits to the proposed Healthcare Provider Safety Brochure to align with the changes in prescriber and pharmacy requirements in the REMS Document. The Applicant should update these materials per the tracked changes and to align with the revised REMS Document.

Patient Safety Card, Patient (b) (4), and REMS Letter: Vaccination reminder to REMS certified prescribers

We have made edits to the proposed Patient Safety Card, Patient (b) (4), and REMS Letter: Vaccination reminder to REMS certified prescribers. The Applicant should update these materials per the

tracked changes and to align with changes made to the REMS Document. The review is ongoing and these REMS materials will be discussed further in a forthcoming review.

REMS Website

We do not find the REMS website as submitted to be acceptable and it will need significant edits. The website, in its entirety, should be updated with the most recent revisions to the REMS Document and REMS materials, i.e. safety brochures, safety cards, and forms. The following additional edits are necessary to the REMS website:

- *The Applicant should remove the following language from the top section of every page:* (b) (4)
- *On the landing page, the Applicant should include sections for all stakeholders and actions they need to take, a section on "What is the ZILBRYSQ REMS," and drug indication. By way of example, the Applicant should refer to the FDA-approved REMS for Camzyos, Zulresso, or Filspari REMS, in public domain.*
- *The Applicant should use the following language when updating the section on the ZILBRYSQ REMS:*
    - (b) (4)

      A REMS is a strategy to manage known or potential (b) (4) *risks associated with a drug.* (b) (4) *is required by the US Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.* (b) (4)
      ZILBRYSQ is only available through a restricted program called the ZILBRYSQ REMS.

3.1.6. Supporting Document

Reviewer's Comments: *The REMS Supporting Document must align with final FDA approved REMS document and labeling. A section on implementation system should be added to the Supporting Document prior to the timetable for submission of assessments and Assessment Plan. Requirements for wholesalers, distributors, and other entities that distribute ZILBRYSQ should be included in the Supporting Document.*

3.1.7. REMS Assessment Plan

The Applicant proposed an Assessment Plan in the Supporting Document.

Reviewer's Comments: *The Applicant's proposed REMS Assessment Plan is currently under review by DMAMES. Any revisions or edits will be addressed in a forthcoming review.*

4. Conclusions and Recommendations

DRM does not find the proposed REMS for zilucoplan as submitted on August 31, 2022, and last amended on November 14, 2022, to be acceptable, as described in this review. Please send the

comments in Section 6 to the Applicant and instruct the Applicant to submit a REMS amendment within 10 business days.

5. Comments for the Applicant

We have the following comments on the proposed REMS submitted August 31, 2022, last amended on November 14, 2022. Review of the REMS proposal is ongoing; therefore, these comments should not be considered final.

REMS Document

See attached redlined REMS Document for reference.

- We do not find the proposed REMS goals to be acceptable. The proposed REMS goal (b) (4) but is not the overall goal of the REMS. Revise the overall goals and objectives to focus on mitigation of occurrence and morbidity associated with meningococcal infections and align with the public health prevention aims of primary and secondary prevention. The REMS goal and objective should be revised as listed below.

  Recommended Revised REMS Goal and Objectives
  The goal of the ZILBRYSQ Risk Evaluation and Mitigation Strategy (REMS) is to mitigate the (b) (4) meningococcal infections.
  (b) (4)
  - Patients are (b) (4) against meningococcal infection prior to starting therapy according to the Advisory Committee on Immunization Practices recommendations
  - Patients are (b) (4) early signs and symptoms of meningococcal infection and the need for immediate medical evaluation
  - Prescribers are (b) (4) early signs and symptoms of meningococcal infection and the need for immediate medical evaluation

- Align the REMS Document with the REMS Document Technical Conformance Guide including addition of risk information to Section 1: Administrative Information and addition of Section 6: Statutory Elements.
- We acknowledge UCB, Inc.'s plan to utilize a third-party logistics provider (3PL) direct to certified specialty pharmacy model for zilucoplan, however requirements for the 3PL related to compliance and auditing will be necessary to be included in the REMS Document. Add a section to participant requirements for wholesaler, distributor, and other entities that distribute Zilbrysq. Add language "and other entities that distribute ZILBRYSQ" when referencing the third-party logistics provider (3PL) distribution model.
- Remove language regardin (b) (4)
- REMS timetable for assessments: The proposed timetable for assessments is not acceptable, as it will not provide adequate data to determine if the REMS is meeting its goal and objectives and

operating as intended. Revise the timeframe to submit REMS Assessments to 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS.

Prescriber Enrollment Form and Pharmacy Enrollment Form

- All attestations which are included in the Prescriber and Pharmacy Enrollment Forms should reflect the language in the REMS Document and REMS requirements. Revise the prescriber and pharmacy attestations within the Prescriber Enrollment Form and Pharmacy Enrollment Form to align with the changes made to the REMS Document. See attached revised Prescriber Enrollment Form and Pharmacy Enrollment Form for reference.

Healthcare Provider Safety Brochure

- We have made edits to the proposed Healthcare Provider Safety Brochure to align with the changes in prescriber and pharmacy requirements in the REMS Document. Update these materials per the tracked changes and to align with the revised REMS Document.

Patient Safety Card, Patient (b) (4), and REMS Letter: Vaccination reminder to REMS certified prescribers

- We have made edits to the proposed Patient Safety Card, Patient (b) (4), and REMS Letter: Vaccination reminder to REMS certified prescribers, however the review of the REMS proposal is ongoing. Update these REMS materials per the tracked changes and to align with changes made to the REMS Document for the next submission.

REMS Website

- We do not find the REMS website as submitted to be acceptable, the website will need significant edits. The website, in its entirety, should be updated with the most recently revisions to the REMS Document and REMS materials, i.e. safety brochures, safety cards, and forms. The following additional edits are necessary to the REMS website:
- Remove the following language from the top section of every page (b) (4)
- On the landing page, include sections for all stakeholders and actions they need to take, a section on "What is the ZILBRYSQ REMS," and drug indication. By way of example, refer to the FDA-approved REMS for Camzyos, Zulresso, or Filspari REMS, in public domain.
- Use the following language when updating the section on the ZILBRYSQ REMS:
    - (b) (4)

      A REMS is a strategy to manage known or potential (b) (4) risks associated with a drug. (b) (4) is required by the US Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. (b) (4) ZILBRYSQ is only available through a restricted program called the ZILBRYSQ REMS.

Supporting Document

- A section on implementation system should be incorporated into the Supporting Document prior to the timetable for submission of assessments and Assessment Plan. Consider including a

description of the REMS Website, REMS Call Center, secure database, plans to detect and address noncompliance with REMS requirements, and steps to improve implementation of and compliance with the requirements of the REMS.

- The REMS Supporting Document should be revised to align with changes made to the REMS Document for the next submission including details related to requirements for wholesalers, distributors, and other entities that distribute ZILBRYSQ.

Resubmission Instructions:

Submit a REMS amendment within 10 business days that addresses these comments.

The following materials contain revisions. If you find these acceptable, update the materials with the revisions and resubmit these materials with the next complete submission. Indicate any new changes you propose as redlined changes in your next submission. Include all formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features.

- REMS Document
- Prescriber Enrollment Form
- Pharmacy Enrollment Form
- Healthcare Provider Safety Brochure
- Patient Safety Card
- Patient (b) (4)
- REMS Letter: Vaccination reminder to REMS certified prescribers

Your complete REMS proposal should be submitted as separate documents in the same submission, should include a Word tracked changes version, a Word clean version, and a .pdf version of each of the documents and appended materials. See the chart below with a summary of required formats for document submission.

Material	**Required Format**
REMS Document	Tracked MS Word, Clean MS Word, Clean PDF version
REMS Supporting Document	Tracked MS Word, Clean MS Word, Clean PDF version
Prescriber Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version
Pharmacy Enrollment Form	Tracked MS Word, Clean MS Word, Clean PDF version
Healthcare Provider Safety Brochure	Tracked MS Word, Clean MS Word, Clean PDF version
Patient Safety Card	Tracked MS Word, Clean MS Word, Clean PDF version

Patient (b) (4)	Tracked MS Word, Clean MS Word, Clean PDF version
REMS Letter: Vaccination reminder to REMS certified prescribers	Tracked MS Word, Clean MS Word, Clean PDF version
REMS Website	Tracked MS Word, Clean MS Word, Clean PDF version
Compiled PDF file that includes the REMS Document and all REMS materials in their final, clean format	PDF version

6. References

1. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Original Submission (Orig-1). August 31, 2022.
2. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Prescribing Information, draft. August 31, 2022.
3. Matthews M. Pre-NDA Type B Meeting Preliminary Comments for Zilucoplan. IND 134340. May 3, 2022.
4. Matthews M. Information Request for Zilbrysq (zilucoplan) regarding format of proposed REMS submission. NDA 216834. November 2, 2022.
5. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. REMS Amendment (sequence 0007). November 14, 2022.
6. Matthews M. Information Request for Zilbrysq (zilucoplan) regarding proposed REMS. NDA 216834. November 18, 2022.
7. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Response to IR (sequence 0008). November 29, 2022.
8. Jawidzik L. Food and Drug Administration. Division of Neurology 1. Midcycle Communication for zilucoplan, NDA 216834. February 27, 2023.
9. Matthews M. Information Request for Zilbrysq (zilucoplan) regarding proposed REMS. NDA 216834. April 5, 2023.
10. UCB, Inc. Zilbrysq (zilucoplan). NDA 216834. Response to IR (sequence 0030). April 13, 2023.
11. Food and Drug Administration. Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research. Guidance Document. REMS Document Technical Conformance Guide. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rems-document-technical-conformance-guide. Published January 04, 2023. Accessed February 22, 2023.

7. Appendix

REMS Document
Prescriber Enrollment Form
Pharmacy Enrollment Form
Healthcare Provider Safety Brochure
Patient Safety Card
Patient (b) (4)
REMS Letter: Vaccination reminder to REMS certified prescribers

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/s/

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