CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761279Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	BLA
Application Number	761279
PDUFA Goal Date	March 30, 2023
OSE TTT #	2022-629
Reviewer Name	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	March 28, 2023
Subject	Evaluation of Need for a REMS
Established Name	Mirikizumab-mrkz
Trade Name	Omvoh
Name of Applicant	Eli Lilly and Company
Therapeutic Class	Interleukin-23 antagonist
Formulation(s)	300 mg/15 mL single-dose vial for intravenous infusion, 100 mg/1 mL single-use prefilled pen for subcutaneous injection
Dosing Regimen	Induction: 300 mg intravenous for at least 30 minutes at Week 0, Week 4, and Week 8 Maintenance: 200 mg subcutaneous every 4 weeks after completion of induction dosage

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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 Omvoh (mirikizumab-mrkz) is necessary to ensure the benefits outweigh its risks. Eli Lilly and Company submitted a Biologic Licensing Application (BLA) 761279 for mirikizumab-mrkz with the proposed indication of the treatment of moderately to severely active ulcerative colitis in adult patients.[1] The risks associated with mirikizumab-mrkz include the following severe adverse events: hypersensitivity reactions, infections, tuberculosis, hepatotoxicity, and the need to avoid the use of live vaccines. The risks associated with mirikizumab-mrkz are similar to other interleukin-23 antagonists. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Gastroenterology (DG) have determined that a REMS is not needed to ensure the benefits of mirikizumab-mrkz outweigh its risks. The risks of hypersensitivity reactions, infections, tuberculosis, hepatotoxicity, and the need to avoid the use of live vaccines will all be managed via warnings and precautions in labeling, similar to other interleukin-23 antagonists approved in the United States. Given the similarity of these risks throughout the product class, additional risk mitigation measures beyond labeling are not necessary to ensure the benefits outweigh the risks of mirikizumab. However, the review team recommends a Complete Response for the application due to manufacturing facility deficiencies observed during inspections. These deficiencies must be resolved prior to approval.[2]

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)[a] Omvoh (mirikizumab-mrkz) is necessary to ensure the benefits outweigh its risks. Eli Lilly and Company (Lilly) submitted a Biologic Licensing Application (BLA) 761279 for mirikizumab-mrkz (hereafter referred to as mirikizumab) with the proposed indication of the treatment of moderately to severely active ulcerative colitis in adult patients. This application is under review in the Division of Gastroenterology (DG) The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Omvoh (mirikizumab), a new molecular entity, is a humanized immunoglobulin 4 (IgG4) monoclonal antibody proposed for the treatment of moderately to severely active ulcerative colitis in adults. The proposed mechanism of action of mirikizumab is binding to the p19 subunit of interleukin-23, acting as a receptor antagonist. Interleukin-23, a member of the interleukin-12 cytokine family, is pro-inflammatory and is a key mediator of intestinal mucosal inflammation. Interleukin-23 is composed of 2 subunits,

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

interleukin-12p40 and interleukin-23p19 (mirikizumab's target). The signaling by interleukin-23 has been implicated in inflammatory intestinal illnesses, including ulcerative colitis.

The induction dose of mirikizumab is 300 mg intravenous (IV) for at least 30 minutes at Week 0, Week 4, and Week 8, and the maintenance dose is 200 mg subcutaneously (SQ) every 4 weeks after completion of induction dosage. Mirikizumab was initially proposed to be available as a 300 mg/15 mL single-dose vial for intravenous infusion, (b) (4) and a 100 mg/mL single-use prefilled pen for subcutaneous injection.[1] Due to use issues observed during a human factors study, the applicant is currently proposing only the 300 mg/15 mL single-dose vial for intravenous injection and 100 mg/mL single-use prefilled pen for subcutaneous injection be available.[3] Mirikizumab is not approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761279 relevant to this review:

- 03/30/2022: BLA 761279 submission for moderately to severely active ulcerative colitis in adult patients received
- 10/05/2023: In a Mid-cycle Communication, the Agency informed the Applicant that while mirikizumab was still under review, based on the currently available data, we do not believe a REMS will be necessary[4]
- 02/14/2023: In the Late-Cycle Meeting Minutes sent to the applicant, the Agency stated that there were no issues related to risk management identified to date[3]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Ulcerative colitis is a chronic inflammatory disease of the large intestine hallmarked by inflammation and ulcers in the mucosal layer of the colon. Symptoms of ulcerative colitis include diarrhea that may include blood, blood in stool, abdominal and/or rectal pain, urgency to defecate, anemia, weight loss, fatigue, fever, colorectal cancer, and growth and development issues in children. Ulcerative colitis can also lead to complications that can require surgery and become life-threatening, such as perforation, toxic megacolon, and severe rectal bleeding.[5b] It is estimated that between 600,000 and 900,000 people in the United States have ulcerative colitis, which can be categorized into mild, moderate, and severe

[b] 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.*

disease.[c] Patients are typically diagnosed in early to middle adulthood (ages 15-30 years old),[6] and can have periods of disease remission and flare.[5d] Patients with moderate colitis experience 4-6 loose, bloody stools daily, mild anemia that does not require blood transfusions (hemoglobin ,>10 g/dL), and abdominal pain that is not severe. These patients experience little to no systemic toxicity and maintain adequate nutrition without weight loss. Patients who have severe disease typically have at least 6 loose, bloody stools daily, severe cramps, weight loss, and present with evidence of systemic toxicity such as fever, tachycardia, anemia, and/or elevated C-reactive protein or erythrocyte sedimentation rate.[7]

3.2. Description of Current Treatment Options

The goal of ulcerative colitis (UC) treatment is to achieve glucocorticoid-free remission demonstrated by complete mucosal healing. As recommended by the American College of Gastroenterology, oral budesonide or oral systemic corticosteroids are used to induce remission. Induction and maintenance of remission treatment options for moderately to severely active disease include anti-integrin agents, Janus-kinase (JAK) inhibitors, tumor necrosis factor (TNF)-α antagonists, interleukin 12/23 antagonists, sphingosine 1-phosphate receptor modulators, and other immunomodulators.[6] While many patients who use a drug successfully in induction therapy often continue on the same drug for maintenance therapy, some patients' response to a specific therapy may decrease over time, necessitating a change in therapy. See Appended table of therapies for moderately to severely active ulcerative colitis.

4. Benefit Assessment

The applicant submitted two Phase 3 trials that make up the focal support of the efficacy and safety of mirikizumab. Study I6T-MC-AMAN (AMAN, NCT 03518086) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group induction study. This 12-week induction study of 1281 subjects randomized 3:1 (mirikizumab to placebo) compared 300 mg intravenous (IV) mirikizumab every 4 weeks to placebo. Study I6T-MC-AMBG (AMBG, NCT 03524092) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group maintenance trial. Study AMBG compared mirikizumab 200 mg subcutaneously (SC) every 4 weeks versus placebo for 40 weeks in 1062 subjects. Both studies used clinical remission as per the modified (3-compent) Mayo score (mMS) as the primary endpoint, which includes the stool frequency subscore (SFS), a rectal bleeding subscore (RBS), and an endoscopic subscore (ES) with friability excluded. Study AMAN defined baseline UC as a score of 4-9 on the mMS, with an ES of at least 2, and study AMBG defined baseline UC as a score of 5-9 on the mMS, with an ES of at least 2. Subjects who were responders to mirikizumab during study AMAN were eligible for the randomized, double-blind portion of study AMBG. "Responders" to mirikizumab were defined as those who achieved clinical response (decrease in mMS of $\geq$2 points with $\geq$30% decrease from baseline, and either a decrease of $\geq$1 Point in RBS from baseline or an RBS of 0 or 1) during AMAN. 1062 subjects who were mirikizumab responders in AMAN were randomized to mirikizumab or placebo in a 2:1 ratio,

[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.*

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

placebo responders in AMAN continued to receive placebo in AMBG, but could be rescued with mirikizumab if necessary, and subjects who did not achieve clinical response in study AMAN received open-label mirikizumab induction therapy and continued to open-label mirikizumab maintenance therapy.

Of note, there was a transcription error in the electronic clinical outcome assessment devices in Poland and Turkey during study AMAN, and therefore, subjects in these countries are excluded from the analysis. The modified intent to treat population analyzed is 1162 subjects with mMS of 4-9.

The primary efficacy endpoint for both studies AMAN and AMBG was clinical remission at Week 12 (AMAN) and Week 40 (AMBG), as determined by the mMS criteria, including the stool frequency subscore (SFS) of 0 or 1, with at least 1 point decrease from baseline, a rectal bleeding subscore (RBS) of 0, and an endoscopic subscore (ES) of 0 or 1 (friability excluded).

In study AMAN, intravenous (IV) mirikizumab 300 mg every 4 weeks was superior to placebo at Week 12, with 23.5% of subjects using mirikizumab achieving clinical remission as opposed to 13.9% of subjects on placebo ($p = 0.00057$). In study AMBG, 50.4% of subjects receiving mirikizumab 20 mg SQ every 4 weeks achieved clinical remission, which was significantly greater than the 26.0% of subjects using placebo who achieved clinical remission ($p < 0.001$).[8]

"Alternate clinical remission," defined as mMS of 0-2, SFS of 0, and ES of 0 or 1 (excluding friability), aligns with DG's preferred definition for clinical remission, was also analyzed and was the focus of the review. Mirikizumab was superior to placebo in this analysis as well, with 24.0% of subjects on mirikizumab achieving alternate clinical remission versus 14.6% of placebo treated subjects ($p < 0.001$) at Week 12 of study AMAN. In study AMBG, at Week 40, 50.7% of mirikizumab-treated subjects achieved alternate clinical remission as compared with 26.6% of placebo-treated subjects ($p < 0.001$).[2e]

5. Risk Assessment & Safe-Use Conditions

The most common (≥2%) adverse reactions seen in the induction phase of mirikizumab treatment are upper respiratory infections and arthralgia. The commonly observed (≥2%) adverse reactions during the maintenance phase are upper respiratory tract infections, injection site reactions, arthralgia, rash, headache, and herpes viral infection.[f] These risks will be outlined in Section 6 of labeling.

While no deaths occurred during the pivotal studies, 2 patients died during the follow-up period of the AMAN study. One patient died of sudden cardiac death Day 5 post colorectal surgery for

[e] 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.*

[f] 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.*

adenocarcinoma, 117 days after the last dose of mirikizumab. This patient discontinued study due to cancer diagnosis. A second patient discontinued study after the second dose of mirikizumab due to an exacerbation of UC. The patient's past medical history included diabetes mellitus Type 2 and obesity. Fifty-nine days after the last dose of mirikizumab, the patient underwent a subtotal colectomy, with postoperative complications including disseminated intravascular coagulation (DIC), severe systemic candidiasis, and sepsis. The patient died 147 days after the last dose of mirikizumab, and the patient may have been immunocompromised due to diabetes and IV steroids used to treat the UC exacerbation. While mirikizumab did not cause the DIC, the clinical reviewer cannot rule out its contribution to increased risk of infection. The single death in study AMBG was due to COVID-19 pneumonia and was 226 days since the last dose of mirikizumab.[9]

5.1. Hypersensitivity Reactions

Four subjects experienced infusion-related hypersensitivity reactions in AMAN. One subject experienced mucocutaneous erythema of the face and neck, increased blood pressure, dyspnea, abdominal pain, and panic. A second subject reported sweating, hyperventilation, vertigo, and low blood pressure. A third experienced a flush over the face, chest, and neck, and the fourth subject experienced mucocutaneous erythema and pruritis on the arms, back, chest, face, and leg. These reactions lasted one day or less. All subjects were discontinued from the study as per protocol.

In the maintenance study ABMG, 30 (7.7%) subjects in the mirikizumab group experienced hypersensitivity reactions, while 7 subjects (3.6%) of subjects in the placebo group experienced these reactions. Seven (1.8%) subjects in the mirikizumab group experienced hypersensitivity reactions that occurred within 24 hours of drug administration, compared to 2 subjects (1.0%) in the placebo group. Hypersensitivity reactions occurred more than 24 hours after drug administration were found in 27 (6.9%) subjects in the mirikizumab group, versus 5 (2.6%) subjects in the placebo group. The most commonly reported reactions were rash, hypersensitivity, and dermatitis. One subject discontinued study due to an injection site hypersensitivity that occurred 5 days after the last mirikizumab dose. This adverse event was qualified as "mild" and resolved after 4 days. Labeling will include information in warnings and precautions regarding the potential for hypersensitivity reactions.

5.2. Infections

In study AMAN, 15.2% of the mirikizumab group reported adverse events of infection, as opposed to 14% reported in the placebo group. Also in study AMAN, two subjects in the mirikizumab group reported pneumonia, as opposed to none in the placebo group. In study AMBG, 24% of subjects taking mirikizumab and 23% of subjects using placebo experienced an infection. One subject using mirikizumab in study AMBG experienced a serious COVID-19 infection. As with other products that can increase the risk of infection due to altering immune response, this will be included in warnings and precautions as well as listed as an adverse reaction in labeling.

5.3. Tuberculosis

Mirikizumab alters immune response and can hinder tuberculosis treatment. Patients with tuberculosis were excluded from clinical trials of mirikizumab. The need to test for tuberculosis prior to initiating will be listed in dosing and administration of mirikizumab labeling, and a warning not to use mirikizumab in patients with active tuberculosis infections, and to initiate treatment of latent tuberculosis prior to starting mirikizumab will be included in warnings and precautions. Information is also provided regarding appropriate treatment for patients with a history of tuberculosis, and to monitor for signs and symptoms of tuberculosis in patients treated with mirikizumab.

5.4. Hepatotoxicity

One subject in both the mirikizumab group and the placebo group in study AMAN experienced alanine aminotransferase (ALN) levels ≥5X upper limit of normal (ULN), and 2 subjects in the mirikizumab group experienced aspartate aminotransferase (AST) ≥5X ULN, while none of the subjects using placebo experienced this elevation. In study AMBG, 3 subjects using mirikizumab reported ALT ≥5X ULN, 3 subjects reported AST elevations ≥5X ULN, some with increases in bilirubin. None of the subjects using placebo experienced any of these hepatic enzyme elevations. In the November 19, 2022, Division of Hepatology and Nutrition Drug-induced Liver (DILI) Team's consult noted only 1 Hy's Law case in approximately 1600 patients who received at least one dose of mirikizumab. The consult noted that there were more cases of ALT and AST elevation in patients who were treated with mirikizumab, as opposed to placebo, and four patients experienced possible DILI due to mirikizumab. As all subjects recovered, the consult recommended including hepatotoxicity in the label's warnings and precautions, along with specific monitoring requirements.[10] The label for mirikizumab reflects this, as prescribers will be directed to obtain baseline liver enzymes and bilirubin enzymes in the dosage and administration section of labeling, and information on hepatoxicity will be listed in warnings and precautions, as well as information on a clinical trial subject who used a longer than recommended induction regimen, which resulted in a drug-induced liver injury. Warnings and precautions in labeling will also include instructions to monitor liver enzymes for at least 24 weeks of treatment.

5.5. Live Vaccine Risk

The directive to complete all age-appropriate vaccines will be noted in labeling in dosage and administration, and labeling will also include the warning to avoid live vaccines as mirikizumab affects the immune system response and can increase the risk of infection following live vaccine administration. Like other products used to treat UC, this will be included in warnings and precautions in labeling.

6. Expected Postmarket Use

Mirikizumab is expected to be prescribed primarily by gastroenterologists, who are expected to be familiar with the risks of interleukin receptor antagonists and products with similar risks for patients with ulcerative colitis. These practitioners are expected to be familiar with appropriate management of adverse events and meet on a regular basis with patients with ulcerative colitis. Mirikizumab will be

administered in clinical settings as an IV infusion during the induction phase, then outpatient by patients or their caregivers as a subcutaneous injection.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for mirikizumab beyond routine pharmacovigilance and labeling, however, the Agency and applicant have agreed on enhanced pharmacovigilance of liver injury to assess incidence of severe liver injury. Additional data is also necessary to characterize the safety of mirikizumab in pregnant and lactating patients, who were excluded from clinical trials, therefore a lactation trial, observational pregnancy outcomes trial, and pregnancy registry will be postmarketing requirements.

8. Discussion of Need for a REMS

The Clinical Reviewers state that the efficacy and safety profile supports approval of mirikizumab, however, until the deficiencies noted in the manufacturing inspection are addressed, the review team has recommended a Complete Response.

Ulcerative colitis is a chronic disease that affects quality of life for patients, and can cause systemic comorbidities, including an increased risk of colon cancer. While there are multiple treatment options currently on the market for ulcerative colitis, for patients who experience a loss of efficacy or inadequate response, a new therapeutic option is needed. DRM and DG considered the risks of mirikizumab and if a REMS is necessary to mitigate them.

The safety risks of mirikizumab are similar to other treatments for ulcerative colitis, including JAK inhibitors, TNF blockers, and another interleukin receptor antagonist on the market. Like the other ulcerative colitis treatments on the market, mirikizumab has the risks of hypersensitivity, increased infections, tuberculosis, hepatotoxicity, and the need to avoid the concomitant use of live vaccines. We expect prescribers to be familiar with the risks and the management of them. The marketed products used to treat ulcerative colitis use labeling to mitigate these risks. Proposed labeling for mirikizumab will include similar language to convey the risks via warnings and precautions and dosing and administration. With the currently available data, mirikizumab requires no further risk mitigation beyond labeling.

9. Conclusion & Recommendations

Based on the available data, DRM and DG agree that a REMS is not necessary to ensure the benefits of tirzepatide outweigh the risks, which can be managed via labeling once the applicant addresses the manufacturing site deficiencies that currently necessitate a Complete Response. Should DG have any concerns of if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. Current Therapies for Moderate to Severely Active UC

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
TNF Blockers				
Infliximab (1998) and Biosimilars	Reducing signs/symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use	5 mg/kg intravenously at baseline, 2, and 6 weeks, then every 8 weeks	Boxed Warning: Increased risk of serious infections (may lead to hospitalization or death) Perform TB test and treat before starting infliximab Lymphoma and other malignancies (potentially fatal) have been reported in children/adolescents treated with TNF blockers Warnings and Precautions: Serious infections including TB, invasive fungal infections, hepatitis B reactivation, malignancies, heart failure, demyelinating disorders, cytopenias, Lupus-like syndrome, hypersensitivity, Cardiovascular/Cerebrovascular reactions	Boxed Warning (BW) Warnings and Precautions (W&P)
Adalimumab (Humira), 2002 and biosimilars	Inducing and sustaining clinical remission in adults with moderately to severely active UC who have had an inadequate response to	Initial Dose (Day 1): 160 m SQ, second dose (Day 15): 80 mg SQ Day 29; begin maintenance	Boxed Warning: See Infliximab W&P: Serious infections including TB, invasive fungal infections, hepatitis B reactivation, malignancies, heart failure,	Boxed Warning Warnings and Precautions

	immunosuppressants	dose 40 mg SQ every 2 weeks	demyelinating disorders, cytopenias/pancytopenia, Lupus-like syndrome, anaphylaxis, or hypersensitivity reactions	
Golimumab (Simponi), 2009	Moderate to severe UC with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy: - inducing and maintaining clinical response - improving endoscopic appearance of the mucosa during induction - inducing clinical remission - achieving and sustaining clinical remission in induction responders	Initial Dose: Week 0: 200 mg SQ Week 2: 100 mg SQ Maintenance: 100 mg SQ every 4 weeks	BW: See infliximab W&P: Serious infections, invasive fungal infections, hepatitis B reactivation, malignancies (lymphoma), congestive heart failure, demyelinating disorders, Lupus-like syndrome, and hypersensitivity reactions	Boxed Warning Warnings and Precautions
Integrin Receptor Antagonist				
Vedolizumab (Entyvio), 2015	Treatment of adult patients with moderately to severely active UC	Weeks 0, 2, and 6: 300 mg infused IV over 30 minutes Then every 8 weeks after	W&P: Infusion related hypersensitivity reactions, Infections, Progressive Multifocal Leukoencephalopathy (PML)	Warnings and Precautions
Janus Kinase (JAK) Inhibitors				
Tofacitinib (Xeljanz/Xeljanz	Adult patients with moderately to	Xeljanz: 10 mg orally twice daily for at least 8 weeks (max. 16	Boxed Warning: -Increased risk of serious bacterial, fungal, viral, and	Boxed Warning Warning and Precautions

XR), 2018 for UC indication	severely active UC, who have had an inadequate response or who are intolerant to TNF blockers	weeks), then 5 mg or 10mg twice daily Xeljanz XR: 22 mg orally once daily for at least 8 weeks (max 16 weeks), then 11 mg once daily	opportunistic infections leading to hospitalization or death, including tuberculosis (TB) -Malignancies (lymphomas and lung cancers) -Higher rate of all-cause mortality, including sudden cardiovascular death -Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) and thrombosis (including pulmonary, deep venous and arterial) Warnings and Precautions: Serious infections, gastrointestinal perforations, changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids	
Upadacitinib (Rinvoq), 2021	Adult patients with moderately to severely active ulcerative colitis, who have had an inadequate response or intolerance to one or more TNF blockers	Induction: 45 mg orally once daily for 8 weeks Maintenance: 30 mg or 15 mg orally once daily (30 mg for patients with refractory, severe, or extensive UC)	Boxed Warning: -Serious infections -Higher rate of all-cause mortality, including sudden cardiovascular death -Malignancies (lymphoma and lung cancer) -Higher rate of major adverse cardiovascular events (MACE), and thrombosis (pulmonary embolism, venous and arterial) Warnings and Precautions: Serious infections, including localized infection, hypersensitivity, GI perforation, laboratory abnormalities in lymphocytes, neutrophils, hemoglobin, liver enzymes	Boxed Warning Warnings and Precautions

			and lipids, embryo-fetal toxicity	
Human Interleukin (IL 12 and 23) Antagonist				
Ustekinumab (Stelara), 2009	Adult patients with moderately to severely active UC	Induction: -Up to 55 kg: 260 mg (2 vials), -Greater than 55 kg to 85 kg: 390 mg (3 vials), -Greater than 85 kg 520 mg (4 vials) Maintenance: (8 weeks post induction dose) 90 mg SQ injection every 8 Weeks	Warnings and Precautions: Serious infections, tuberculosis, malignancies, hypersensitivity reactions, reversible posterior leukoencephalopathy syndrome (PRES), and noninfectious pneumonia	Warnings and Precautions
Sphingosine 1-Phosphate (S1P) Receptor Modulator				
Ozanimod (Zeposia), 2020	Adult patients with moderately to severely active UC	Initiation: -Days 1-4: 0.23 mg orally once daily -Days 5-7: 0.46 mg orally once daily Maintenance: Day 8 and thereafter: 0.92 mg orally once daily	Warnings and Precautions: Infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, fetal risk, increased blood pressure, respiratory effects (may cause a decline in pulmonary function), macular edema	Warnings and Precautions

**Adapted from the ongoing clinical review of mirikizumab, March 30, 2023.*

10.2. References

1. Eli Lilly and Co., Proposed Prescribing Information for Mirikizumab, February 24, 2023.
2. Division of Gastroenterology Unireview of Mirikizumab (BLA 761279), March 30, 2023.
3. Richards, Kelly. BLA 761279 Late-Cycle Meeting Minutes, February 14, 2023, DARRTS ID # 5126486.
4. Richards, Kelly, BLA 761279 Mid-cycle Communication, October 5, 2022, DARRTS ID #5056019.
5. Ulcerative Colitis. March 10 2023, Updated September 2020. https://www.niddk.nih.gov/health-information/digestive-diseases/ulcerative-colitis/all-content

6. Rubin D, Ananthakrishnan, A.N., et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. *The AMerican Journal of Gastroenterology*. March 2019 114(3):384-413.
7. Mangement of moderate to severe ulcerative colitis in adults. Updated June 23, 2022. https://www.uptodate.com/contents/management-of-moderate-to-severe-ulcerative-colitis-in-adults
8. Eli Lilly and Company, Summary of Clinical Efficacy of Mirikizumab, March 08, 2022.
9. Eli Lilly and Company, Summary of Clinical Safety of Mirikizumab, March 17, 2022.
10. Hayashi, P., Lan, L., Division of Hepatology and Nutrition Drug-induced Liver Injury Team Consult Review of Mirikizumab, November 19, 2022, DARRTS ID# 5080876.

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