CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	216956
PDUFA Goal Date	October 14, 2023
Nexus TTT #	2022-2364
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Director	Laura Zendel, PharmD
Review Completion Date	October 12, 2023
Subject	Evaluation of Need for a REMS
Established Name	Etrasimod
Trade Name	Velsipity
Name of Applicant	Pfizer, Inc.
Therapeutic Class	Sphingosine 1-phosphate receptor modulator
Formulation(s)	2 mg oral tablet
Dosing Regimen	2 mg orally once daily

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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 Velsipity (etrasimod) is necessary to ensure the benefits outweigh its risks. Pfizer, Inc. submitted a New Drug Application (NDA) 216956 for Velsipity with the proposed indication for the treatment of (b) (4) moderately to severely active ulcerative colitis in patients. If approved, the indication will be for the treatment of moderately to severely active ulcerative colitis in adults.[1] The risks associated with Velsipity include increased risk of infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, macular edema, increased blood pressure, fetal risk, malignancies, posterior reversible encephalopathy syndrome, immune system effects after stopping Velsipity, additive immune system effects from prior immunosuppressive products, and a decline in pulmonary function. 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 Velsipity outweigh its risks. The risks of increased risk of infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, macular edema, increased blood pressure, fetal risk, malignancies, posterior reversible encephalopathy syndrome, immune system effects after stopping Velsipity, additive immune system effects from prior immunosuppressive products, and a decline in pulmonary function will be mitigated via labeling in warnings and precautions. Other sphingosine 1-phosphate receptor modulators also use the same warnings and precautions, and given the similarity of the risks, additional mitigation measures beyond labeling are not necessary to ensure the benefits outweigh the risks of Velsipity.

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] Velsipity (etrasimod) is necessary to ensure the benefits outweigh its risks. Pfizer, Inc. submitted a New Drug Application (NDA) 216956 for etrasimod with the proposed indication for the treatment of (b) (4) moderately to severely active ulcerative colitis.[2] 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

Velsipity (etrasimod), a new molecular entity, is a sphingosine 1-phosphate (S1P) receptor modulator, with selective activity at S1P 1, 4, and 5. Etrasimod reversibly and partially blocks the capacity of

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

lymphocytes leaving lymphoid organs by acting as a receptor antagonist, thereby reducing the quantity of lymphocytes in peripheral blood. With a lower number of lymphocytes circulating in the blood, this reduces the number of available lymphocytes to be recruited to sites of inflammation and lowers active lymphocyte levels in tissue. This reduces cytokine release that promotes inflammation and may result in less tissue damage.[3] Velsipity is proposed as a 2 mg oral tablet once daily for the treatment of moderately to severely active ulcerative colitis.

Velsipity is not currently approved in any jurisdiction, but the European Medicines Agency has accepted the Marketing Authorization Application for etrasimod for patients with moderately to severely active ulcerative colitis, and the applicant expects a decision in the first half of 2024.[4]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216956 relevant to this review:

- 10/14/2022: NDA 216956 submission for the treatment of moderately to severely active ulcerative colitis (b) (4)
- 04/03/2023: In a Mid-cycle Communication, the Agency informed the Applicant that while Velsipity was still under review, based on the currently available data, we do not believe a REMS will be necessary[5]
- 07/03/2023: In the Late-Cycle Meeting Background Package sent to the applicant, the Agency stated that there were no issues related to risk management identified to date[6]

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 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.[7,b] 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 disease.[c] Patients are typically diagnosed in early to middle adulthood (ages 15-30 years old),[8] and can

[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.*

[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.*

have periods of disease remission and flare.[7,d] 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.[9]

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. Additional goals in the treatment and management of UC are to reduce signs and symptoms of active disease, decrease underlying mucosal inflammation, and prevent short-term complications such as severe bleeding and bowel perforation and long-term complications including colon cancer. Clinicians determine therapy based on the severity and extent of the disease. As recommended by the American College of Gastroenterology, oral budesonide or oral systemic corticosteroids are used to induce remission. Corticosteroids are not recommended for long-term use due to toxicity associated with chronic use. 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.[8] 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 Appendix 10.1 for a table of currently approved therapies for moderately to severely active ulcerative colitis.

4. Benefit Assessment

The applicant submitted 2 clinical studies in support of the proposed indication of Velsipity, Study APD334-301 (NCT03945188), and Study APD334-302 (NCT03996369), hereafter referred to as "Study 301" and "Study 302." Study 301 was a 52-week, double-blinded, placebo-controlled, treat-through study of 433 patients randomized 2:1 (n=289, 144) to receive Velsipity 2 mg daily or placebo; study 302 was a 12-week, double-blind, placebo-controlled induction trial of 354 subjects randomized 2:1 (n= 238, 116) to receive Velsipity 2 mg daily or placebo. Study 301 and 302 included subjects ages 16-80 years of age, who had an inadequate response, loss of response, or intolerance to at least one conventional therapy for ulcerative colitis, including oral 5-ASA, corticosteroids, thiopurines, biologic therapy, or JAK inhibitors. Subjects also must have been diagnosed with UC ≥ 3 months prior to screening, confirmed by endoscopic and histologic evidence, have active UC with ≥ 10 cm rectal involvement confirmed by endoscopy, and have moderately to severely active UC defined as a modified Mayo score (mMS) of 4-9, with an endoscopic score (ES) of ≥2 and a rectal bleeding subscore (RBS) ≥1. The mMS is comprised of the ES, RBS, and stool frequency subscore (SFS). The primary endpoint for both studies was clinical

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

remission at Week 12 and in Study 301, a co-primary endpoint was maintaining clinical remission at Week 52. Patients who met the UC worsening criteria in Study 301 were eligible to enter the open-label extension study APD334-303 (NCT03950232), and if they did not meet the criteria, patients continued on the randomized treatment for an additional 40 weeks for a total duration of 52 weeks. Clinical remission was defined by the applicant as an SFS of 0 or SFS of 1 with a $\geq$1 point decrease from baseline, RBS of 0, and ES of 0 or 1 (excluding friability). The applicant's definition of clinical remission differed from the Agency's preferred definition of clinical remission of SFS of 0 or 1 (no requirement for a ≥ 1 point decrease from baseline), RBS of 0, and ES of 0 or 1 (excluding friability). The Agency's definition of remission was used in the efficacy analysis.[10]

Table 1. Efficacy Results for the Co-Primary Endpoints of Study 301

Parameter	Velsipity 2 mg QD (n=274)	Placebo (n=134)
Clinical Remission at Week 12, n (%)	75 (27.4)	10 (7.5)
95% Confidence Interval, Treatment Difference		20.1 (13.2, 27.0)
P-value		<0.0001
Clinical Remission at Week 52, n (%)	89 (32.5)	9 (6.7)
95% Confidence Interval, Treatment Difference		27.5 (18.7, 32.7)
P-value		<0.0001

Adapted from ongoing Unireview of Velsipity (etrasimod), NDA 216956

In Study 301, subjects using Velsipity 2 mg once daily experienced a statistically significantly greater remission rate both at 12 and 52 weeks.

Table 2. Efficacy Results for the Primary Endpoint of Study 302

Parameter	Velsipity 2 mg QD (n=221)	Placebo (n=112)
Clinical Remission at Week 12, n (%)	58 (26.2)	17 (15.2)
95% Confidence Interval, Treatment Difference		11.2 (2.7, 19.8)
P-value		0.010

Adapted from ongoing Unireview of Velsipity (etrasimod), NDA 216956

In Study 302, subjects taking Velsipity 2 mg once daily experienced clinical remission at a statistically significantly greater rate than those taking placebo at Week 12.

The clinical reviewer states in the ongoing Unireview of Velsipity states that "etrasimod demonstrated efficacy in achieving the coprimary endpoints of clinical remission at Week 12 and Week 52, compared to placebo."[e]

5. Risk Assessment & Safe-Use Conditions

Studies 301 and 302 were submitted in support of safety of Velsipity, along with study APD334-003 (NCT02447302), a Phase 2, a 12-week, double-blind, placebo-controlled, parallel-group induction study of 156 subjects randomized 1:1:1 (n=52, 50, 54) to receive etrasimod 1 mg daily, etrasimod 2 mg daily, or placebo. Safety data from the 2 mg group from the 12-week Studies 302 and 003 were pooled to better assess adverse events. An "All UC" safety data pool includes data from the 3 studies, open label studies APD334-303, APD334-005 (NCT02536404), and Study ES101002 (NCT04176588) and Study APD334-308 (NCT04706793), which were studies in Asia that were ongoing at time of submission. Due to the open-label and ongoing nature of these studies, they were not included in the primary safety evidence, but were assessed for rare events.

The most commonly occurring (>5%) adverse events observed during the 52-week study were headache, elevated liver enzymes, and dizziness, and the most commonly occurring (>5%) adverse events during the 12-week induction studies were headache, elevated liver enzymes, dizziness, and nausea. [f]

No deaths in subjects using Velsipity were reported in the 52-week study 301 or in the 12-week studies 302 and 003. A 33-year-old male in Study APD334-303 taking Velsipity died due to a neuroendocrine tumor of unknown primary site. The subject had received placebo in Study 301, prior to enrollment in Study 303, and took 24.3 weeks of Velsipity in Study 303.[11]

The risks of increased risk of infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, macular edema, increased blood pressure, malignancies, posterior reversible encephalopathy syndrome, and a decline in pulmonary function are considered class effects and labeling will reflect this. As class adverse events, these were considered adverse events of special interest in the Velsipity development studies. Immune system effects after stopping an S1P have been noted in other products, as have additive immune system effects from prior immunosuppressive products and will be addressed in Warnings and Precautions. While not an AESI observed in the studies, fetal risk is a known adverse event associated with S1P receptor modulators and will also be included in labeling. Sections 5.1-5.7 of this review cover AESIs and a potential fetal risk case that were seen in the Velsipity clinical efficacy and safety studies.

In the ongoing Unireview of Velsipity, the Clinical Reviewer states that, "The size of the safety database was adequate to support approval of the proposed dosing regimen. However, the size of the controlled

[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.*

52-week trial does not allow for a definitive characterization of the potential for rare, serious safety concerns (e.g., mortality, malignancy, progressive multifocal leukoencephalopathy, cryptococcal meningitis) that have been observed in S10 receptor modulators…labeling is considered adequate to communicate these risks and provide appropriate risk mitigation."[12]

5.1. Increased Risk of Infections

Study protocol included reporting of severe, opportunistic, and herpes simplex and zoster infections as AESI.

In Study 301, 8 (2.8%) subjects in the Velsipity group experienced these infections, while 7 (4.9%) subjects in the placebo group experienced one of these infections. Overall infection rate in subjects in Study 301 that were treated with Velsipity was 24.9% versus 22.2% in placebo. In the pooled 12-week safety data, 2 subjects in both the Velsipity (0.6%) and 2 subjects in the placebo group (1.3%) experienced an infection.

The increased risk of infections will be listed in Warnings and Precautions of labeling.

5.2. Bradyarrhythmia and Atrioventricular Conduction Delays

Bradycardia was defined as one or more of the following: heart rate <40 beats per minute (bpm) with or without symptoms, if the event was associated with clinical symptoms, or if the event led to the subject withdrawing from the study. AV conduction delay was defined at least one of the following: second-degree AV block or higher, the PR interval was > 230 ms, or the event included clinical symptoms that were potentially related on review.

In Study 301, 0.7% of subjects in the Velsipity experienced a first or second degree Mobitz type I AV block and 1% of subjects had treatment initiation day bradycardia. No subjects in the placebo group experienced either AESI. In the pooled 12-week safety data, 2.0% of subjects in the Velsipity group experienced bradycardia, 1.8% experienced hypertension and 0.8% experienced a first or second degree Mobitz type I AV block. In placebo-treated subjects in the same studies, 1.8% of subjects experienced hypertension.

The risk will be included in Warnings and Precautions in labeling.

5.3. Liver Injury

To meet the definition of an AESI in the Velsipity studies, the subject must have experienced any liver transaminase (alanine transferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and gamma-glutamyl transferase (GGT)) elevation >5 times the upper limit of normal (ULN) or sustained elevation > 3 times ULN, and bilirubin elevation of >2 times ULN without Gilbert's syndrome.

In Study 301, 4.5% of Velsipity-treated subjects experienced ALT elevations to 3-times the ULN, compared to (2.1%) of subjects using placebo. In the pooled 12-week data, (2.5%) subjects taking

Velsipity had an elevation in ALT to 3-times the ULN and 0.5%) placebo-using subjects had an ALT elevation to 3 times the ULN.

This risk will be addressed in Warnings and Precautions in labeling.

5.4. Macular Edema

Macular edema is a risk associated with other S1P receptor modulators and can lead to decreased visual acuity.

One subject experienced macular edema that required discontinuation. In subjects with OCT thickness reported at baseline, 17% of Velsipity-treated subjects, versus 8% in the placebo group, had central foveal thickness (CFT) increases of $\geq$40 µm, the Applicant's criteria for macular edema based on CFT increase.

The risk of macular edema will be communicated in Warnings and Precautions in labeling, as well as the recommendation to obtain a baseline evaluation of the macula and fundus near the beginning of etrasimod treatment as well as periodically during treatment.

5.5. Increased Blood Pressure

Hypertension was defined in Velsipity development as sustained systolic blood pressure (SBP) elevation > 160 mmHg, sustained diastolic blood pressure > 100 mmHg, or medication was added to control a subject's blood pressure.

In Study 301, 9 subjects taking Velsipity (3.1%) met the hypertension criteria while no subjects in the placebo group experienced hypertension.

The risk of increased blood pressure will be included in Warnings and Precautions of labeling.

5.6. Fetal Risk

In Study 301, one case of anembryonic gestation was seen in a subject in the Velsipity group.

This risk will be communicated via Warnings and Precautions in labeling.

5.7. Respiratory Effects

Respiratory adverse events were defined in study protocols as defined as airflow obstruction (FEV_1, FVC) defined as a decrease from baseline of > 25% or accompanied by relevant symptoms and decreased gas exchange (DLCO) – defined as a decrease from baseline of > 25% or accompanied by relevant symptoms.

In Study 201, 1 subject in the both the Velsipity (0.3%) and placebo (0.7%) groups experienced an airflow obstruction during the study.

The risk of respiratory effects will be communicated in Warnings and Precautions in labeling.

6. Expected Postmarket Use

Velsipity is expected to be prescribed primarily by gastroenterologists, who are expected to be familiar with the risks of sphingosine 1-phosphate receptor modulators 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. Velsipity will be taken as an outpatient oral medication by patients.

7. Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for Velsipity beyond routine pharmacovigilance and labeling.

7.1. Other Proposed Risk Management Activities

The review team proposed the following postmarketing requirements, which will be issued at approval: a milk-only lactation trial in lactating women who have received Velsipity to assess concentrations of etrasimod in breast milk, a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Velsipity, and another pregnancy study using a different design from the prospective pregnancy registry to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age/preterm births in women exposed to Velsipity.[12]

Reviewer's Comments: *We note that these other activities proposed by the applicant are outside of the scope of our review and defer to Divisions of Pharmacovigilance and Epidemiology for review and input.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Velsipity on the basis of the efficacy and safety information currently available.

Ulcerative colitis is a chronic disease that decreases patients' quality of life while increasing the chances of hospitalization with life-threatening complications. Pfizer, Inc. submitted a New Drug Application (NDA) 216956 for Velsipity with the proposed indication for the treatment of (b) (4) moderately to severely active ulcerative colitis in patients. (b) (4)

Like other S1P modulators used to treat UC, Velsipity increases the risks of infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, macular edema, increased blood pressure, fetal risk,

malignancies, posterior reversible encephalopathy syndrome, immune system effects after stopping Velsipity, additive immune system effects from prior immunosuppressive products, and pulmonary function decline. DG and DRM considered these risks and if a REMS was necessary to mitigate them. The safety concerns with etrasimod use are similar to other marketed S1P modulators, which use labeling to convey the risks and risk mitigation measures in Warnings and Precautions in labeling. Risk mitigation measures recommended in labeling include routine labs such as complete blood count and liver tests, as well as other evaluations such as baseline electrocardiogram, eye exams, skin exam, and blood pressure including considerations for consultation with other healthcare providers (cardiology, ophthalmology). Given the similarity of risks among S1P inhibitors, we expect prescribers to be familiar with the risks and risk mitigation recommendations. A Medication Guide detailing risks and safe use of etrasimod will be included in labeling to communicate the risks to patients. With the currently available data, additional risk management measures beyond labeling are not necessary to ensure the benefits outweigh the risks of Velsipity.

9. Conclusion & Recommendations

Based on available data, DRM and DG agree that a REMS is not necessary to ensure the benefits of Velsipity outweigh the risks, which can be managed via labeling. Should DG have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. Current Therapies for Moderately 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	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	Boxed Warning (BW) Warnings and Precautions (W&P)

	eliminating corticosteroid use		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	
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 immunosuppressants	Initial Dose (Day 1): 160 m SQ, second dose (Day 15): 80 mg SQ Day 29; begin maintenance dose 40 mg SQ every 2 weeks	Boxed Warning: See Infliximab W&P: Serious infections including TB, invasive fungal infections, hepatitis B reactivation, malignancies, heart failure, demyelinating disorders, cytopenias/pancytopenia, Lupus-like syndrome, anaphylaxis, or hypersensitivity reactions	Boxed Warning Warnings and Precautions
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	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

	- improving endoscopic appearance of the mucosa during induction - inducing clinical remission - achieving and sustaining clinical remission in induction responders			
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 XR), 2018 for UC indication	Adult patients with moderately to severely active UC, who have had an inadequate response or who are intolerant to TNF blockers	Xeljanz: 10 mg orally twice daily for at least 8 weeks (max. 16 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	Boxed Warning: -Increased risk of serious bacterial, fungal, viral, and 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:	Boxed Warning Warning 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 and lipids, embryo-fetal toxicity	Boxed Warning Warnings and Precautions
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

**Table taken from DRM review of Omvoh (mirikizumab, BLA 761279), March 28, 2023.*

10.2. References

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