Mirikizumab-mrkz (OMVOH)

Intravenous and Subcutaneous Injection in Ulcerative Colitis

National Drug Monograph

March 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 5ASA, 5-aminosalicylic acid; 6MP, 6-mercaptopurine; AZP, azathioprine; bIMM, biologic immunomodulator; DB, double-blind; GC, glucocorticoid; IL-##i, interleukin-## inhibitor; IMM, immunomodulator; INT, intolerance; IR, inadequate response; IV, intravenous(ly); JAKi, Janus kinase inhibitor; LOR, loss of response; MIA, medical inadvisability; MN, multinational; OL, open-label; PC, placebo-controlled; PNR, primary nonresponse; RCT, randomized clinical trial; SC, subcutaneous(ly); TBD, to be decided; UC, ulcerative colitis

FDA Approval Information

Description / Mechanism of Action

- First interleukin (IL)-23 inhibitor (IL-23i) to be approved for ulcerative colitis (UC)
- Humanized IgG4 monoclonal antibody selective for the p19 subunit of human IL-23 cytokine.[i] Inhibits binding of cytokine to the IL-23 receptor.

Indication Under Review in This Document

- Treatment of moderately to severely active UC in adults.

Pre-treatment Evaluations and Immunizations

- Patients should be evaluated for tuberculosis (TB) before initiating therapy.
- Baseline liver enzymes and bilirubin levels should be obtained.
- All age-appropriate vaccinations should be administered according to current immunization guidelines.

Dosage Regimen Under Review

- *Induction Therapy*: 300 mg by IV infusion at Weeks 0, 4, and 8
- *Maintenance Therapy*: 200 mg by SC injection (two consecutive injections of 100-mg each) at Week 12, then every 4 weeks thereafter

Dosage Forms Under Review

- *IV Infusion*: Injection, 300 mg/15 mL (20 mg/mL) solution in a single-dose vial
- *SC Injection*: 100 mg/mL solution in a single-dose prefilled pen

Efficacy Considerations

- No active-controlled trials have been performed.

- Two phase 3 placebo-controlled randomized clinical trials (RCTs) supported the efficacy of mirikizumab in patients with moderate to severe, active UC.[ii] The first trial showed efficacy of mirikizumab induction (300 mg IV every 4 weeks for 12 weeks) in achieving clinical remission at Week 12. The second trial showed that SC mirikizumab (200 mg every 4 weeks for 40 weeks) achieved or maintained clinical remission at Week 40 (total 52 weeks).
- A phase 2 dose-ranging RCT provided supportive evidence of efficacy.[iii]

Phase 3 Randomized Clinical Trials

- Table 1 summarizes the methods of the phase 3 RCTs.

Table 1 Methods of Phase 3 RCTs

Topic	Induction Trial (LUCENT-1)	Maintenance Trial (LUCENT-2)
Study Design	12-wk MN DB PC RCT (3:1) Randomization was stratified by treatment failure with biologic or tofacitinib, baseline disease activity, and geographic region Multiplicity adjustments for 7 major secondary end points	40-wk MN DB PC withdrawal RCT (2:1) Wk-12 clinical responders in the induction trial were re-randomized in the maintenance RCT, except placebo clinical responders in the induction trial continued placebo in the maintenance trial. Randomization was stratified by treatment failure with biologic or tofacitinib, remission status at Wk 12 of the induction trial, GC use, and geographic region
Major Entry Criteria	Inclusion Criteria: • Age 18–18 y • Moderate to severe, active UC at screening • IR, LOR or inability to take ≥ 1 GC or IMM (conventional treatment failure) or bIMM or JAKi (biologic or tofacitinib treatment failure) Exclusion Criteria: • Previous exposure to IL-12i, IL-23p40i, or IL-23p19i • Treatment failure with ≥3 different biologics	Inclusion Criteria: • Completed induction trial, regardless of clinical response or treatment assignment
Interventions	• Mirikizumab 300 mg IV Q4W for 12 wks • Placebo Stable doses of 5ASA, oral GCs, or AZP, 6MP, or MTX	• Mirikizumab 200 mg SC Q4W for 40 wks • Placebo (mirikizumab withdrawal) Tapered doses of oral GCs in clinical responders Patients who had LOR at ≥ Wk 12 discontinued study treatment and received 3 doses of OL mirikizumab (300 mg IV Q4W) as rescue therapy.
Primary Efficacy Measure(s)	Clinical remission at Wk 12, defined using • Modified Mayo criteria, per protocol • Alternate definition, preferred per FDA (multiplicity controlled major secondary end point): a stool frequency subscore of 0 or 1, a rectal-bleeding subscore of 0, and an endoscopic subscore of 0 or 1 (excluding friability) Significant p-value: 0.00125 99.875% confidence intervals	Clinical remission at Wk 40, defined using modified Mayo criteria and alternate FDA criteria as in the induction trial Significant p-value: 0.05 95% confidence intervals
Baseline Patient Characteristics	Age 42 y Male 58%	—

Topic	Induction Trial (LUCENT-1)	Maintenance Trial (LUCENT-2)
	Overweight, obese, or extremely obese 41% Previous treatment failure with biologic 41%, TNFi 35%, vedolizumab 19%, or tofacitinib 3%	

Results

Table 2 Week-12 Efficacy results from the induction trial (LUCENT-1)

Outcome	Mirikizumab 300 mg IV	PBO	RR (95% CI)	AAE (99.875% CI)	NNT (95% CI)	Q
Clinical remission, n/N (%)	210/868 (24.2)	39/294 (13.3)	1.8 (1.33, 2.50)	111 (32, 191)	10 (7, 17)	M†
Clinical remission per FDA, n/N (%)	222/868 (25.6)	43/294 (14.6)	1.7 (1.30, 2.36)	NR	10 (7, 17)	M†
Endoscopic remission, n/N (%)	315/868 (36.3)	62/294 (21.1)	1.7 (1.36, 2.18)	154 (63, 245)	7 (5, 11)	H
H-E Mucosal Improvement	235/868 (27.1)	41/294 (13.9)	1.9 (1.43, 2.63)	134 (55, 214)	8 (6, 13)	M†
IBDQ remission, n/N (%)	499/868 (57.5)	117/294 (39.8)	1.4 (1.24, 1.68)	181 (118, 244)	6 (5, 9)	H

AAE, anticipated absolute effects per 1000 patients; H-E, histologic-endoscopic; IBDQ, Inflammatory Bowel Disease Questionnaire; a measure of quality of life; score range 32–224; remission was defined as a total score of ≥ 170 on a scale of 32–224); Q, GRADE quality of evidence; RR, relative risk

† Downgraded for imprecision (optimal information size not met for relative risk reduction of 25%)

Table 3 Week-40 (Week-52 Total) Efficacy results from the maintenance trial (LUCENT-2)

Outcome	Mirikizumab 200 mg SC	PBO	RR (95% CI)	AAE (95% CI)	NNT (95% CI)	Q
Clinical remission, n/N (%)	182/365 (49.9)	52/179 (25.1)	1.7 (1.34, 2.21)	232 (152, 312)	5 (4, 9)	M†
GC-free clinical remission, n/N (%)	164/365 (44.9)	39/179 (21.8)	2.1 (1.53, 2.78)	213 (135, 291)	5 (4, 7)	M†
Maintenance of clinical remission, n/N (%)	91/143 (63.6)	24/65 (36.9)	1.7 (1.23, 2.42)	248 (104, 392)	4 (3, 8)	M†
Endoscopic remission, n/N (%)	214/365 (58.6)	52/179 (29.1)	2.0 (1.58, 2.58)	285 (202, 368)	4 (3, 5)	M†
H-E Mucosal Improvement	158/365 (43.3)	39/179 (21.8)	2.0 (1.47, 2.69)	199 (121, 276)	5 (4, 8)	M†
IBDQ remission, n/N (%)	264/365 (72.3)	77/179 (43.0)	1.7 (1.40, 2.01)	285 (201, 370)	4 (3, 5)	H

Footnotes: See Table 2.

Table 4 Onset of Benefit and Adequate Therapeutic Trial

Trial	Outcome Measure	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
LUCENT-1	Remission of symptoms	4	—
LUCENT-1	CFB in bowel urgency	4	—
LUCENT-2	CFB† in bowel urgency	16	32

CFB, change from baseline

† From Week 4 of induction trial

Safety Considerations

Table 5 Safety Profile from US Prescribing Information

Domain	Adverse Events
Boxed Warnings	None
Contraindications	History of serious hypersensitivity reaction to mirikizumab-mrkz or excipients
Other Warnings / Precautions	Infections, TB, hepatotoxicity, immunizations (avoid live vaccines; no data on response to live or non-live vaccines)
Common Adverse Events (≥ 2%) During Induction	Upper respiratory tract infections, arthralgia

Common Adverse Events (≥ 2%) During Maintenance	Upper respiratory tract infections, injection site reactions, arthralgia, rash, headache, herpes viral infection

Table 6 Selected Safety Results, Induction Trial (LUCENT-1)

Outcome	Mirikizumab 300 mg IV	PBO
Serious adverse event, n/N (%)	27/958 (2.8)	17/321 (5.3)
Death, n/N (%)	0	0
Discontinuation due to adverse event, n/N (%)	15/958 (1.6)	23/321 (7.2)
Any adverse event	426/958 (44.5)	148/321 (46.1)

Table 7 Selected Safety Results, Maintenance Trial (LUCENT-2)

Outcome	Mirikizumab 200 mg SC	PBO
Serious adverse event, n/N (%)	13/389 (3.3)	15/192 (7.8)
Death, n/N (%)	0	1/192 (0.5)
Discontinuation due to adverse event, n/N (%)	6/389 (1.5)	16/192 (8.3)
Any adverse event	251/389 (64.5)	132/192 (68.8)

Evidence Gaps

- Hospitalization or readmission
- Functional ability / Disability

Network Meta-analyses

- No relevant network analyses were found.

Other Therapeutic Options

Table 8 Biologic and Targeted Synthetic Immunomodulators for Moderate to Severe Active UC in Adults

Drug	Formulary Status	CFU Place in Therapy	FDA Place in Therapy in UC	2020 AGA Guideline[iv] Place in Therapy
IL-23i				
Mirikizumab-mrkz	TBD	TBD	No prerequisite therapy required	FDA-approved in 2023
TNFis				
Infliximab / Biosimilar	PA-F,* -abda biosimilar is the preferred infliximab product	—	IR to conventional therapy Also for mucosal healing and eliminating GC use	*Induction, Biologic-naïve*: Suggested over adalimumab
Golimumab	NonF	—	GC dependence and an IR or INT to oral 5ASAs, oral GCs, AZP, or 6MP	*Induction*: Recommended over no treatment; no active-comparator recommendations.
Adalimumab / Biosimilar	PA-F,* -bwwd biosimilar is the preferred adalimumab product	—	No prerequisite therapy required	*Induction, Biologic-naïve*: Alternative to infliximab (e.g., hypersensitivity) or vedolizumab

Drug	Formulary Status	CFU Place in Therapy	FDA Place in Therapy in UC	2020 AGA Guideline[iv] Place in Therapy
Integrin Receptor Antagonist				
Vedolizumab inj for IV use	PA-F	After TNFi or infliximab / BSM therapy	No prerequisite therapy required	*Induction, Biologic-naïve*: Suggested over adalimumab
Vedolizumab inj for SC use	PA-F	Clinical response after Wk 6 following IV induction doses at Wks 0 and 2 or is receiving IV doses to maintain clinical remission	*Maintenance*: May start SC injections Q2W at Wk 6 after IV induction doses at Wks 0 and 2 or switch to SC injections Q2W in place of next scheduled Q8W maintenance IV infusion	FDA-approved in 2023
IL-12/23i				
Ustekinumab / Biosimilar	NonF	TNFI MIA and vedolizumab MIA, INT, or IR Or after TNFI	No prerequisite therapy required	*Induction, Infliximab-exposed (particularly for PNR)*: Suggested over vedolizumab or adalimumab
JAKis				
Tofacitinib	NonF	TNFI MIA and vedolizumab MIA, INT, or IR Or after TNFI	IR or INT to ≥ 1 TNFi	*Biologic-naïve*: Use in clinical or registry study; no recommendation‡ *Induction, Infliximab-exposed (particularly for PNR)*: Suggested over vedolizumab or adalimumab
Upadacitinib	NonF	Same as for tofacitinib	IR or INT to ≥ 1 TNFi	FDA-approved in 2022
Sphingosine-1 Phosphate Receptor Modulators				
Etrasimod	NonF	NA†	No prerequisite therapy required	FDA-approved in 2023
Ozanimod	NonF	NA†	No prerequisite therapy required	FDA-approved in 2021

5ASA, 5-aminosalicylic acid; 6MP, 6-mercaptorpurine; AZP, azathioprine; BSM, biosimilar; CFU, Criteria for Use; CS, corticosteroid; INT, intolerance; IR, inadequate response; MIA, medical inadvisability; PNR, primary nonresponse (i.e., no response to induction therapy)
* Restricted to providers appropriate for prescribing TNFis.
† Monograph provides potential place in therapy
‡ Knowledge gap at the time the guideline was published

Other Considerations

- A pharmacokinetic study showed small reductions in bioavailability with increases in body mass index and increases in clearance with increased body weight.[v]. The authors concluded that no dosage modifications due to patient factors were required.
- Mirikizumab showed promising efficacy for moderate to severe, active Crohn's disease in a phase 2 dose-ranging trial.[vi]
- A phase 3 trial (OASIS-1) showed that mirikizumab was safe and efficacious in the treatment of plaque psoriasis for up to 52 weeks.[vii]

Projected Place in Therapy

- **Potential Place in Therapy in VHA**. Mirikizumab-mrkz is a well-tolerated IL-23i that showed efficacy in the induction and maintenance of clinical remission in patients with moderate to severe, active UC who had an

inadequate response, intolerance, or medical inadvisability to conventional, biologic, or tofacitinib therapy (moderate to high quality evidence of small effects). Its place in therapy relative to other biologic and targeted synthetic immunomodulators approved for UC is uncertain. It offers another mechanism of action to the limited number of available treatment options for UC.

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