Risankizumab-rzaa (SKYRIZI) in Ulcerative Colitis
National Drug Monograph
February 2025
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: AAE, Anticipated absolute effect for achieving the outcome; AC, active-controlled; AZP, azathioprine; CD, Crohn's disease; cIMM, conventional immunomodulator; CO, crossover; CSA, cyclosporine A; DB, double-blind; ES, endoscopy subscore; GC, glucocorticoid; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HS, hidradenitis suppurativa; ID, insufficient data; INT, intolerance; IR, inadequate response; JAKi, Janus kinase inhibitor; JIA, juvenile idiopathic arthritis; LOR, loss of response; MIA, medical inadvisability; mMS, modified Mayo score; MN, multinational; NNT, Number needed to treat for one additional patient to benefit; PBO, placebo; PC, placebo-controlled; PJIA, polyarticular juvenile idiopathic arthritis; PK, pharmacokinetic; PPsO, plaque psoriasis; PsA, psoriatic arthritis; Q, GRADE quality of evidence (M = Moderate, L = Low); RA, rheumatoid arthritis; RBS, rectal bleeding subscore; RCT, randomized clinical trial; RIS, risankizumab; RR, relative risk; S1PRM, sphingosine-1-phosphate-receptor modulator; TB, tuberculosis; UC, ulcerative colitis; UV, uveitis

Prescribing Considerations

Description / MOA	Second interleukin-23 inhibitor that selectively binds to the p19 subunit (IL-23p19i) approved for ulcerative colitis (UC), following mirikizumab-mrkz
Indication Under Review[1]	Treatment of moderately to severely active UC
Procedures and Monitoring	*Pretreatment*: Obtain liver enzymes and bilirubin levels; evaluate for tuberculosis (TB) infection; administer guideline-recommended vaccinations *During Induction, Up to ≥ 12 Weeks of Treatment*: Liver enzymes and bilirubin levels *Subsequent Treatment*: Liver enzymes and bilirubin levels according to routine patient management
Dosage Regimen	*Induction*: 1200 mg IV infusion over at least 2 hours at Weeks 0, 4, and 8 *Maintenance*: 180 mg or 360 mg SC at Week 12 then every 8 weeks thereafter. Use the lowest effective dosage needed to maintain therapeutic response.
Dosage Forms Under Review	*IV Infusion*: 600 mg/10 mL single-dose vial *SC Injection*: 90 mg/mL single-dose prefilled syringe; 180 mg/1.2 mL and 360 mg/2.4 mL (each 150 mg/mL) single-dose prefilled cartridges for use with on-body injector

Efficacy Considerations

Trial	**INSPIRE Substudy 2**[2,3]
Design	12-week phase 3, MN DB PC induction RCT (2:1 randomization), including a phase 3 induction substudy and a phase 2b induction substudy consisting of a dose-ranging study following by an open-label substudy Clinical remission was defined as a modified Mayo score (mMS, range 0–9) stool frequency subscore of ≤ 1 and not greater than baseline; rectal bleeding subscore (RBS) of 0; and endoscopy subscore (ES) of ≤ 1 without friability
Population	Moderately to severely active UC, mMS of 5–9, and ES of 2–3. Inadequate response (IR) or intolerance (INT) to oral aminosalicylates, GCs, conventional immunomodulators (cIMMs) alone; ≥ 1 biologic, Janus kinase inhibitor (JAKi), and/or sphingosine-1-phosphate receptor modulator (S1PRM); or combination of conventional and advanced therapies. No prior exposure to ustekinumab (p40) or IL-23 (p19) inhibitors. Responders were eligible to enroll in the COMMAND maintenance trial. Nonresponders were eligible for an additional 12 weeks of induction therapy. Intent-to-treat population = 975 patients; baseline characteristics not reported. In 966 patients described in the prescribing information,[1] the median mMS was 7 with 37% having mMS > 7 (severe) and 69% with ES of 3. A total of 499 patients (52%) had IR or INT to ≥ 1 targeted immunomodulator (biologics [97%], JAKis [18%], or S1PRM).
Intervention	Risankizumab 1200 mg IV infusion at Weeks 0, 4, and 8
Comparator	Placebo

Allowed Co-therapies	Aminosalicylates (73%), GCs (stable dose ≤ 20 mg/d prednisone equivalent; 36%), cIMMs (16%)
Results	**Induction Efficacy Results at Week 12**

Outcome	RIS 1200	PBO	RR (95% CI)	AAE per 1000 (95% CI)	Q
Clinical remission, n/N (%)	155/650 (20.3)	26/325 (6.2)	3.0 (2.01, 4.42)	140 (100, 180)	L$^{\alpha\beta}$
Endoscopic remission, n/N (%)	69/650 (10.6)	11/325 (3.4)	3.1 (1.68, 5.84)	72 (42, 102)	M$^{\beta}$
UC-related hospitalizations	5/650 (0.8)	18/325 (5.5)	0.1 (005, 0.37)	–48 (–73, –22)	M$^{\beta}$

Blue text indicates a significant difference. L, low; M, moderate; Q, GRADE quality of evidence
α, Downgraded for indirectness (surrogate of final clinical outcome) and imprecision (optimal information size not met)
β, Downgraded for imprecision

- Patient-reported outcomes also showed significantly better improvements with risankizumab vs placebo, including no bowel urgency (44.1% vs 27.7%; 95% CI, 10.3-22.4), no nocturnal bowel movements (67.3% vs 43.1%; 95% CI, 17.9-30.5), and no abdominal pain (35.8% vs 26.5%; 95% CI, 3.4-15.3).[2]

Trial	**COMMAND Substudy 1[4]**
Design	52-week phase 3, MC DB PC maintenance RCT Stratified by history of inadequate response (IR) to advanced therapy, last risankizumab induction dose (600, 1200, or 1800 mg IV), and clinical remission status. IR was defined as ≥ 30% and ≥ 2-point reduction from baseline on the adapted Mayo score and ≥ 1-point reduction on RBS or RBS of ≤ 1. Loss of response (LOR) was defined as RBS of ≥ 1 point more than the Week 0 value or an endoscopic subscore of 2 or 3.
Population	Enrolled in induction trial; clinical response to risankizumab at Week 12 or 24
Intervention	Risankizumab 180 mg SC every 8 weeks Risankizumab 360 mg SC every 8 weeks
Comparator	Placebo
Other Therapies	Patients on GCs were required to taper by Week 8. Starting at Week 16, patients in either treatment group could receive open-label risankizumab (a single IV dose then 360 mg every 8 weeks) for LOR.
Results	**Maintenance Efficacy Results at Week 52**

Outcome	RIS 180	RIS 360	PBO	RR (95% CI) RIS 180	RR (95% CI) RIS 360	AAE per 1000 (95% CI) or Diff (95% CI) RIS 180	AAE per 1000 (95% CI) or Diff (95% CI) RIS 360
Clinical remission, n/N (%)	72/179 (40.2)	70/186 (37.6)	46/183 (25.1)	1.6 (1.18, 2.18)	1.5 (1.10, 2.04)	163 (61, 266)	142 (40, 245)
Endoscopic remission, n/N (%)	41/179 (23.2)	45/186 (24.3)	27/183 (14.8)	1.6 (1.00, 2.41)	1.6 (1.07, 2.52)	95 (8, 182)	96 (9, 182)
≥ 1 UC-related hospitalization, patients / 100 person-years	0.6	1.2	3.1	—	—	–2.5 (–5.8, 0.8)	–1.8 (–5.5, 1.8)

Blue text indicates a significant difference. ID, insufficient data; L, low; M, moderate; Q, GRADE quality of evidence
α, Downgraded for indirectness to clinical outcome
β, Downgraded for imprecision

- Patient-reported outcomes also showed significantly better improvements with risankizumab vs placebo, including no bowel urgency (44.1% vs 27.7%; 95% CI, 10.3-22.4), no nocturnal bowel movements (67.3% vs 43.1%; 95% CI, 17.9-30.5), and no abdominal pain (35.8% vs 26.5%; 95% CI, 3.4-15.3).

Safety Considerations	
Boxed Warnings	None
Contraindications	History of serious hypersensitivity reaction to risankizumab-rzaa or excipients
Other Warnings	Hypersensitivity reactions, infections, TB, hepatotoxicity during induction, avoid live vaccines
Most Common AEs (≥ 3%)	*Induction*: Arthralgia *Maintenance*: Arthralgia, pyrexia, injection site reactions, rash
Geriatric Use	Limited data. 103 UC patients were aged ≥ 65 years.
Drug Interactions	*Cytochrome P450 Substrates*: No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed.

Treatment Alternatives

Table 1 Treatment Alternatives and Place in Therapy of Agents Indicated for Moderate to Severe Active UC

DRUG	VANF	PBM Guidance for Use in UC	FDA	ACG GUIDELINES (2019)[5]	AGA GUIDELINES (2020)[6]
IL-23is					
Risankizumab-rzaa	No	TBD	No prerequisite therapy specified for UC Also approved for PPsO, PsA, and CD	Predated drug approval	Predated drug approval
Mirikizumab-mrkz	No	CFU: • TNFi MIA and vedolizumab failure, OR • TNFi failure OR • LOR to infliximab / biosimilar* AND • Failure of tofacitinib or upadacitinib, AND etrasimod or ozanimod, AND ustekinumab *Infliximab is the preferred TNFi in UC	No prerequisite therapy specified for UC		
TNFis					
Adalimumab (ADA)-bwwd	Yes	ADA-bwwd and INF-abda are the preferred TNFis in VHA. Restricted to providers appropriate for prescribing TNFis	No prerequisite therapy specified in UC *Limitations of Use*: Effectiveness of ADA has not been established in patients who had LOR or INT to TNFis. Also approved for AS, CD, HS, JIA, PPsO, PsA, RA, and UV	Recommend TNFi using ADA or GOL, or INF with a thiopurine, for induction of remission (strong recommendation, high quality evidence; moderate quality evidence for AZP) Continue TNFi for maintenance of remission in patients with previously moderately to severely active UC (strong recommendation, moderate quality evidence)	Biologic-naïve: Suggest using INF rather than ADA for induction of remission (conditional recommendation, moderate quality evidence) *Note*: ADA may be a reasonable choice, especially in patients with less severe disease who value the convenience of self-administered SC injections more than the relative efficacy of medications.
Infliximab (INF)-abda	Yes		IR to conventional therapy Also for mucosal healing and eliminating GC use Also approved for AS, fistulizing CD, CD, PPsO, PsA, and RA (not PJIA)		
Golimumab (GOL)	No		GC dependence and IR or INT to oral 5ASAs, oral GCs, AZP, or 6MP Also approved for AS, PJIA, PsA, and RA (not PPsO)		
INF-dyyb for SC use	No	CFU: Clinical responders to induction, stable on IV infliximab maintenance, or unable to accommodate or comply with IV maintenance schedule	Maintenance treatment of moderately to severely active UC following treatment with an IV infliximab product		

DRUG	VANF	PBM Guidance for Use in UC	FDA	ACG GUIDELINES (2019)[5]	AGA GUIDELINES (2020)[6]
			Also approved for maintenance treatment of CD		
Alpha-4-beta-7-Integrin Receptor Blocker					
Vedolizumab (VEDO) for IV use	Yes / PA-F	CFU: • TNFi MIA OR • Failure of one TNFi OR • LOR to infliximab / biosimilar OR • maintenance of clinical response or remission achieved with CSA rescue therapy when immunomodulator maintenance is MIA (used for acute, severe UC)	No prerequisite therapy specified for UC Also approved for CD	Induction of remission (strong recommendation, moderate quality evidence) Induction of remission after failure of TNFi therapy (strong recommendation, moderate quality evidence) Continue vedolizumab for maintenance of remission of previously moderately to severely active UC (strong recommendation, moderate quality evidence)	Recommend using VEDO over no treatment (strong recommendation, moderate quality evidence) Biologic-naïve: Suggest using VEDO rather than ADA for induction of remission (conditional recommendation, moderate quality evidence)
VEDO for SC use	Yes / PA-F	CFU: Clinical response after Week 6 following IV induction doses at Weeks 0 and 2 or is receiving IV doses to maintain clinical remission	At Week 6, patients may remain on VEDO IV or switch to SC after receiving two IV induction doses at Weeks 0 and 2. OR patients currently responding to IV VEDO after Week 6 may be switched to SC injection starting with the next scheduled IV infusion.		
JAKis					
Tofacitinib (TOF)	No	CFU: • TNFi MIA and vedolizumab failure OR • Failure of TNFi OR • LOR to TNFi	IR or INT to ≥ 1 TNFi Also approved for AS, PJIA, PsA, and RA	Induction of remission after failure of TNFi therapy (strong recommendation, moderate quality evidence) Continue TOF for maintenance of remission of previously moderately to severely active UC (strong recommendation, moderate quality evidence)	*Guidelines predated safety update for TOF regarding increased risks of mortality, MACE, malignancy, and thrombosis.* Previously exposed to INF, especially in primary nonresponders: Suggest TOF over VEDO or ADA for induction of remission after exposure to INF (conditional recommendation, low quality evidence)
Upadacitinib (UPA)	No	Same as for TOF	IR or INT to ≥ 1 TNFi Also approved for AS, AD, CD, nr-axSpA, PJIA, PsA, and RA	Predated drug approval	Predated drug approval

DRUG	VANF	PBM Guidance for Use in UC	FDA	ACG GUIDELINES (2019)[5]	AGA GUIDELINES (2020)[6]
IL-12/23i					
Ustekinumab (UST)	No	CFU: • TNFi MIA and vedolizumab failure OR • Failure of one TNFi OR • LOR to INF / biosimilar	No prerequisite therapy specified for UC Also approved for CD, PPsO, and PsA	Predated drug approval	Previously exposed to INF, especially in primary nonresponders: Suggest UST over VEDO or ADA for induction of remission (conditional recommendation, low quality evidence)
Sphingosine 1–Phosphate Receptor Modulators (S1PRMs)					
Etrasimod	No	Monograph Place in Therapy: • Failure of INF and VEDO	No prerequisite therapy specified for UC	Predated drug approval	Predated drug approval
Ozanimod	No				

VHA Place in Therapy	
Evidence Summary	• The place in therapy of risankizumab in UC is uncertain given a lack of head-to-head trials. Risankizumab was shown to be efficacious in inducing and maintaining clinical remission and endoscopic remission in 12-week and 52-week phase 3 placebo-controlled RCTs (small–medium effects; very low–moderate quality evidence). • Evidence gaps include relative efficacy and safety from head-to-head trials, long-term safety of risankizumab in UC, and real-world experience in UC.
Potential Use in VHA	• Risankizumab-rzaa may be used for the treatment of moderately to severely active UC in patients who have medical inadvisability to, or mechanistic failure of, a TNFi, or pharmacokinetic failure of infliximab/biosimilar (the preferred TNFi in UC).

Prepared: February 2025.

Contact person: Francine Goodman, PharmD, BCPS, National Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

References

1. SKYRIZI (risankizumab-rzaa) injection for subcutaneous or intravenous use [prescribing information online]. North Chicago, IL: AbbVie. June 2024. Available at: skyrizi_pi.pdf (rxabbvie.com). Accessed July 12, 2024.
2. Risankizumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Efficacy and Safety in the Randomized Phase 3 INSPIRE Study. Gastroenterol Hepatol (N Y). 2023 Dec;19(12 Suppl 9):9-10. PMID: 38445187; PMCID: PMC10910380.
3. Louis E, Schreiber S, Panaccione R, Bossuyt P, Biedermann L, Colombel JF, Parkes G, Peyrin-Biroulet L, D'Haens G, Hisamatsu T, Siegmund B, Wu K, Boland BS, Melmed GY, Armuzzi A, Levine P, Kalabic J, Chen S, Cheng L, Shu L, Duan WR, Pivorunas V, Sanchez Gonzalez Y, D'Cunha R, Neimark E, Wallace K, Atreya R, Ferrante M, Loftus EV Jr; INSPIRE and COMMAND Study Group. Risankizumab for Ulcerative Colitis: Two Randomized Clinical Trials. JAMA. 2024 Jul 22:e2412414. doi: 10.1001/jama.2024.12414. Epub ahead of print. PMID: 39037800; PMCID: PMC11264075.
4. Louis E, Schreiber S, Panaccione R, Bossuyt P, Biedermann L, Colombel JF, Parkes G, Peyrin-Biroulet L, D'Haens G, Hisamatsu T, Siegmund B, Wu K, Boland BS, Melmed GY, Armuzzi A, Levine P, Kalabic J, Chen S, Cheng L, Shu L, Duan WR, Pivorunas V, Sanchez Gonzalez Y, D'Cunha R, Neimark E, Wallace K, Atreya R, Ferrante M, Loftus EV Jr; INSPIRE and COMMAND Study Group. Risankizumab for Ulcerative Colitis: Two Randomized Clinical Trials. JAMA. 2024 Jul 22:e2412414. doi: 10.1001/jama.2024.12414. Epub ahead of print. PMID: 39037800; PMCID: PMC11264075.
5. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413. doi: 10.14309/ajg.0000000000000152. PMID: 30840605.
6. Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020 Apr;158(5):1450-1461. doi: 10.1053/j.gastro.2020.01.006. Epub 2020 Jan 13. PMID: 31945371; PMCID: PMC7175923.