Risankizumab-rzaa (SKYRIZI) in Crohn's Disease
National Drug Monograph Addendum
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

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.

FDA Approval Information

Description / Mechanism of Action

- Risankizumab-rzaa is the first interleukin-23 (IL-23) p19 antagonist and the fourth targeted therapy approved for Crohn's disease (CD).[1]

Indication Under Review in This Document

- Treatment of moderately to severely active CD in adults.

Dosage Regimen

- Before initiating treatment, obtain liver enzymes and bilirubin levels, evaluate for tuberculosis (TB) infection, and complete all guideline-recommended vaccinations. Monitor liver enzymes and bilirubin during induction for up to at least 12 weeks of therapy.
- *Induction*: 600 mg IV infusion over at least 1 hour at Weeks 0, 4, and 8.
- *Maintenance*: 180 mg or 360 mg SC at Week 12 then every 8 weeks thereafter. Use the lowest effect dosage to maintain therapeutic response.

Dosage Forms Under Review

- *Intravenous Infusion, Injection*: 600 mg/10 mL (60 mg/mL) per single-dose vial
- *Injection (kits)*: 180 mg/1.2 mL and 360 mg/2.4 mL (each 150 mg/mL) per single-dose prefilled cartridge with an On-Body Injector that adheres to the skin and administers each dose over a period of up to 5 minutes. (On-Body Injectors are also known as wearable injectors.)
    - The On-Body Injector must be kept at least 12 inches away from electronic devices including cell phones during administration and should not be exposed to magnetic resonance (e.g., magnetic resonance imaging). The effects of potential electronic interference are unknown. If used next to other electrical equipment, the patient will need to check that the device is operating normally.

Clinical Evidence Summary

Efficacy Considerations

- No head-to-head randomized clinical trials have been conducted.
- Risankizumab-rzaa was shown to be efficacious in induction of clinical remission (defined as Crohn's disease activity index [CDAI] < 150) of moderately to severely active CD in two phase 3 placebo-controlled RCTs, ADVANCE and MOTIVATE.[2] ADVANCE included patients with or without prior biologic failure (i.e., intolerance or inadequate response), and MOTIVATE included only patients with prior biologic failure. Patients without prior biologic failure in ADVANCE had intolerance or

inadequate response to conventional therapies including aminosalicylates, conventional immunomodulators (cIMMs; e.g., azathioprine, 6-mercaptopurine, subcutaneous or intramuscular methotrexate), budesonide (oral locally acting corticosteroid) and/or systemically acting corticosteroids. Exclusions included patients with active hepatitis B or hepatitis C. Active hepatitis B virus (HBV) infection was defined as hepatitis B surface antigen (HBsAg) positive or hepatitis B core antibody (HBcAb) positive. Active hepatitis C virus (HCV) infection was defined as detectable HCV RNA with positive anti-HCV antibody (HCVAb). During the trials, patients were not allowed to take oral corticosteroids at doses higher than prespecified limits (prednisone or equivalent > 20 mg/day; budesonide > 9 mg/day) or conventional immunomodulators if not taken for ≥ 42 days prior to baseline or were not taking stable doses for ≥ 35 days prior to baseline.

- Efficacy data are summarized in Table 1 and Table 2.

Table 1 Selected Week-12 Efficacy Results From the Phase 3 Clinical Trials

Outcome	RIS 600	PBO	Relative Risk (95% CI)	Difference (95% CI)
Conventional Therapy Failures or Biologic Failures (ADVANCE)				
CDAI Clinical Remission, n/N (%)	152/336 (45.2)	43/175 (24.6)	1.8 (1.4, 2.4)	20.6 (12.0, 28.5)
Endoscopic Response, n/N (%)	135/336 (40.2)	21/175 (12.0)	3.3 (2.2, 5.1)	28.2 (20.6, 34.9)
Without Previous Biologic Failure (ADVANCE)				
CDAI Clinical Remission, n/N (%)	69/141 (48.9)	18/78 (23.1)	2.1 (1.4, 3.3)	25.8 (12.5, 37.2)
Endoscopic Response, n/N (%)	71/141 (50.4)	10/78 (12.8)	3.9 (2.2, 7.2)	37.6 (25.3, 47.5)
With Previous Biologic Failure (ADVANCE)				
CDAI Clinical Remission, n/N (%)	83/195 (42.6)	25/97 (25.8)	1.7 (1.1, 2.4)	26.8 (15.0, 37.1)
Endoscopic Response, n/N (%)	64/195 (32.8)	11/97 (11.3)	2.9 (1.6, 5.2)	21.5 (11.5, 29.9)
Biologic Failures (MOTIVATE)				
CDAI Clinical Remission, n/N (%)	80/191 (41.9)	37/187 (19.8)	2.1 (1.5, 3.0)	22.1 (12.9, 30.8)
Endoscopic Response, n/N (%)	55/191 (28.8)	21/187 (11.2)	2.6 (1.6, 4.1)	17.6 (9.6, 25.4)

CDAI, Crohn's disease activity index (scale 0–600; remission was defined as CDAI < 150)

Table 2 Absolute Effects for Achieving Selected Outcomes at Week 12

Outcome Measure	Trial	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
CDAI Clinical Remission	ADVANCE	197 (98, 344) more	5 (4, 9)	H
Endoscopic Response	ADVANCE	276 (144, 492) more	4 (3, 5)	H
CDAI Clinical Remission	MOTIVATE	218 (99, 396) more	5 (4, 8)	H
Endoscopic Response	MOTIVATE	180 (67, 348) more	6 (4, 11)	M[α]

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; Q, GRADE quality of evidence (H = High, M = Moderate)

[α] Downgraded for imprecision (wide CIs).

  - The effect sizes (treatment differences vs placebo, 95% CI) for achieving clinical remission were similar in patients without biologic failure (25.8% [12.5, 37.2]) relative to the subgroup with prior biologic failure (26.8% [15.0, 37.1]).
  - For endoscopic response, the effect sizes were numerically higher in patients without previous biologic failure than those with previous biologic failure: 37.6 (25.3, 47.5) vs 21.5 (11.5, 29.9).

- Substudy 1 of a 52-week phase 3 placebo-controlled withdrawal RCT with re-randomization (FORTIFY SS1) confirmed that, in patients who achieved clinical response at Week 12 in ADVANCE or MOTIVATE, risankizumab-rzaa (180 mg or 360 mg) was efficacious in maintaining clinical remission.[3]
  - The percentage of patients in CDAI clinical remission at Week 0 / Week 52 were 61% / 55% and 59% / 52% vs 59% / 41% with risankizumab-rzaa 180 mg and 360 mg vs placebo (withdrawal group), respectively. The adjusted treatment differences vs withdrawal / placebo for CDAI

clinical remission were 15% (95% CI 5, 25) and 15% (4, 25) for risankizumab-rzaa 180 mg and 360 mg, respectively. The clinical remission rate of 41% in the withdrawal / placebo group indicated durability of risankizumab-rzaa benefits continuing from ADVANCE and MOTIVATE.
    - The 360-mg dose but not the 180-mg dose showed significant efficacy for the non-US primary outcome measure of stool frequency and abdominal pain score clinical remission.
    - Risankizumab-rzaa maintained clinical remission in the subgroups without and with previous biologic failure, with numerically higher rates in the subgroup without previous biologic failure.
    - Risankizumab-rzaa was significantly better than placebo in achieving clinically important improvements in health-related and functional outcomes in ADVANCE, MOTIVATE, and FORTIFY SS1.[4]
    - Antidrug antibodies occurred in 2% (4/224) of risankizumab-rzaa groups combined and 4% (4/92) of the withdrawal / placebo group.[3]
- A 12-week phase 2 placebo-controlled RCT in patients with previous biologic exposure provided supportive evidence of induction efficacy for risankizumab-rzaa 180 mg.[5]
- Risankizumab-rzaa was shown to maintain clinical remission (71%) and clinical response (81%) in a 26-week (total 52 weeks of treatment) open-label extension study of the phase 2 induction RCT.[6]

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) was 4 weeks.[2]
- The duration of an adequate therapeutic trial (time to peak CDAI clinical remission or CDAI clinical response rate) was 12 weeks.[2]

Safety Considerations in Crohn's Disease

- Except for the occurrence of hepatotoxicity during induction therapy, the safety profile for risankizumab-rzaa in CD was similar to those observed for previously approved indications (plaque psoriasis and psoriatic arthritis).

Safety Profile from US Prescribing Information

- Boxed Warnings: None.
- **Contraindications**: History of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients
- Other Warnings / Precautions
    - *Hepatotoxicity in treatment of Crohn's disease*. Drug-induced liver injury has occurred during induction therapy. Monitor liver enzymes and bilirubin at baseline, during induction, and up to at least 12 weeks of treatment. Then monitor as per routine patient management. Consider other treatment alternatives in patients with evidence of liver cirrhosis.
    - Hypersensitivity reactions
    - Infections
    - Tuberculosis (TB)
    - Avoid use of live vaccines
- Common Adverse Events in Crohn's Disease
    - *Induction*: Upper respiratory infections, headache, arthralgia
    - *Maintenance*: Arthralgia, abdominal pain, injection site reactions, anemia, pyrexia, back pain, arthropathy, urinary tract infection

Safety Results from Clinical Trials:

- Table 5 summarizes selected safety data from the phase 3 clinical trials.

Table 3 Selected Adverse Events, Induction Therapy

Outcome	RIS 600	PBO
ADVANCE		
Death, n/N (%)	0 (0)	2 (1)
Serious Adverse Event, n/N (%)	27 (7)	28 (15)
Discontinuation Due to Adverse Event	9 (2)	14 (8)
Hepatic events	9 (2)	4 (2)
MOTIVATE		
Death, n/N (%)	0 (0)	0 (0)
Serious Adverse Event, n/N (%)	10 (5)	26 (13)
Discontinuation Due to Adverse Event	2 (1)	17 (8)
Hepatic events	1 (< 1)	2 (1)

Source: 2

Evidence Gaps

- Survival / Mortality
- Hospitalization or readmission
- Patient Satisfaction

Network Meta-analyses

- One network meta-analysis included the phase 2 and the three phase 3 risankizumab trials (ADVANCE, MOTIVATE, and FORTIFY SS1).[7] The results from ADVANCE were reported in an abstract, and FORTIFY SS1 results were reported in a press release and included in analyses for induction outcomes but not for maintenance of clinical remission. Risankizumab was significantly better than vedolizumab in induction of clinical remission in patients with previous biologic exposure (Table 3) and was ranked second highest after adalimumab (Table 4).
- Risks of serious adverse events and infection were not reported for risankizumab.

Table 4 Network Meta-analysis Comparing Risankizumab with Other Targeted Therapies for Induction of Clinical Remission in Moderately to Severely Active CD

Comparison	NMA Estimate, OR (95% CrI)	Q
Biologic-naïve (K = 15,† N = 2931)		
Infliximab vs Risankizumab	2.07 (0.63, 6.87)	L
Infliximab + TP vs Risankizumab	3.43 (0.87, 13.54)	VL
Adalimumab vs Risankizumab	1.38 (0.51, 3.69)	L
Adalimumab + TP vs Risankizumab	0.78 (0.21, 2.85)	VL
Ustekinumab vs Risankizumab	0.83 (0.31, 2.21)	L
Risankizumab vs Vedolizumab	1.10 (0.38, 3.19)	L
Risankizumab vs Certolizumab	2.19 (0.77, 6.21)	L
Biologic-exposed (K = 10,‡ N = 2479)		
Risankizumab vs Ustekinumab	1.34 (0.79, 2.27)	L
Risankizumab vs Adalimumab	0.74 (0.35, 1.57)	VL
Risankizumab vs Vedolizumab	**2.10 (1.12, 3.92)**	**M**

Source: 7
Q, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low); **T**
† 1 trial for risankizumab
‡ 3 trials for risankizumab

Table 5 Overall SUCRA Rankings for Induction of Clinical Remission

Rank	Intervention	SUCRA
Biologic-naive		
1	Infliximab + Azathioprine	0.96
2	Infliximab	0.81
3	Adalimumab	0.67
4	Ustekinumab	0.58
5	Risankizumab	0.49
6	Vedolizumab	0.45
7	Certolizumab	0.15
Biologic-exposed		
1	Adalimumab	0.92
2	Risankizumab	0.77
3	Ustekinumab	0.53
4	Vedolizumab	0.23

Source: 7
SUCRA, Surface under the cumulative ranking curve (range, 0–100)

Other Therapeutic Options

- The general steps in systemic drug therapy of moderate to severe luminal CD according to the 2021 American Gastroenterological Association (AGA) practice guidelines[8] are summarized in Table 6, and the place in therapy of targeted therapies for CD are summarized in Table 7. Risankizumab-rzaa was not included in the AGA guideline.

Table 6 Systemic Pharmacotherapies for Adult Outpatients with Moderate to Severe Luminal CD According to the 2021 AGA Practice Guideline

Phase in Therapy	Treatment Alternatives (SOR, QE)	Comments (SOR, QE)
Induction, Not Otherwise Specified	Recommend **TNFI** (strong, moderate)	Suggest against the use of natalizumab. May consider natalizumab in patients who are JC virus antibody negative, will adhere to monitoring, and who put a high value on potential benefits and lower value on PML risk. There is a lack of comparative data for biologics vs methotrexate. Suggest against the use of *oral* methotrexate monotherapy (conditional, very low). Suggest against thiopurine monotherapy (conditional, very low). Recommend against 5-ASA or sulfasalazine (strong, moderate).
	Suggest **vedolizumab** (conditional, low)	
	Recommend **ustekinumab** (strong, moderate)	
	Recommend **biologic monotherapy** be preferred over **thiopurine monotherapy** (strong, moderate).	
	Suggest **subcutaneous or intramuscular methotrexate monotherapy** (conditional, moderate)	
	Suggest **corticosteroid** (conditional, moderate)	
	No recommendation for the use of **ustekinumab** or **vedolizumab**, **each in combination with thiopurines or methotrexate**, over biologic monotherapy (knowledge gap)	Ustekinumab and vedolizumab are less immunogenic than infliximab and therefore their use in combination with a cIMM may not reduce immunogenicity.
	Suggest that **early introduction of a biologic** with or without a cIMM be preferred over delaying their use until after failure of mesalamine and/or corticosteroid (conditional, low).	Early introduction of a biologic ± cIMM may result in overtreating and/or causing additional harm or costs with limited benefit, whereas a step-up approach may cause harm from disease progression by delaying appropriate therapy.
Induction, Biologic-naïve	Recommend that **infliximab** be preferred over **certolizumab** (strong, moderate)	
	Recommend that **adalimumab** be preferred over **certolizumab** (strong, moderate)	
	Recommend that **ustekinumab** be preferred over **certolizumab** (strong, moderate)	
	Suggest that **vedolizumab** be preferred over **certolizumab** (conditional, low)	
Induction, Naïve to Biologics and cIMMs	Suggest **infliximab + thiopurines** be preferred over **infliximab monotherapy** (conditional, moderate)	Indirect evidence suggests that infliximab + methotrexate may be better than infliximab monotherapy. TDM with infliximab monotherapy may be able to achieve the same benefits and improve safety (e.g., infections, lymphoma) vs combination infliximab + cIMM.
	Suggest **adalimumab + thiopurine** be preferred over **adalimumab monotherapy** (conditional, very low)	Indirect evidence suggests that adalimumab + methotrexate may be better than adalimumab monotherapy.

Phase in Therapy	Treatment Alternatives (SOR, QE)	Comments (SOR, QE)
Induction, TNFI Primary Nonresponse	Recommend **ustekinumab** (strong, moderate)	
	Suggest **vedolizumab** (conditional, low)	
Induction, Infliximab Secondary Nonresponse	Recommend **adalimumab** (strong, moderate)	
	Recommend **ustekinumab** (strong, moderate)	
	Suggest **vedolizumab** (conditional, low)	
Maintenance, Not Otherwise Specified	Recommend **TNFI** (strong, moderate; low for certolizumab)	Suggest against the use of natalizumab. Suggest against the use of *oral* methotrexate monotherapy (conditional, very low). Recommend against 5-ASA or sulfasalazine (strong, moderate). Recommend against corticosteroid (strong, moderate) Ustekinumab and vedolizumab are less immunogenic than infliximab and therefore their use in combination with a cIMM may not reduce immunogenicity.
	Suggest **vedolizumab** (conditional, moderate)	
	Recommend **ustekinumab** (strong, moderate)	
	Suggest **subcutaneous or intramuscular methotrexate monotherapy** (conditional, moderate)	
	No recommendation for the use of **ustekinumab** or **vedolizumab**, **each in combination with thiopurines or methotrexate**, over biologic monotherapy (knowledge gap)	
Maintenance, Quiescent CD or Corticosteroid-induced Remission	Suggest **thiopurine monotherapy** (conditional, low)	Recommend against the use of corticosteroid.
	No recommendation for **withdrawal** of either the cIMM or biologic over continuing combination therapy	Recommend against 5-ASA or sulfasalazine (strong, moderate)

5-ASA, 5-Aminosalicylic acid; cIMM, Conventional immunomodulator; JC, John Cunningham; QE, Quality of evidence; SOR, Strength of recommendation

Table 7 Place in Therapy of Treatment Alternatives for Moderate to Severe, Active CD

Drug	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
Risankizumab-rzaa	TBD	TBD	1st-line	—	Hepatic injury during induction	Less clinical experience in CD May be preferred over vedolizumab in patients who have comorbid plaque psoriasis or psoriatic arthritis, require faster onset (4 weeks vs 10 weeks), or refuse in-clinic IV maintenance infusions.
TNFIs	Yes	N/A	1st-line *Infliximab*: Inadequate response to conventional therapy	Recommended for induction and maintenance Certolizumab is less preferred than adalimumab, infliximab, ustekinumab, and vedolizumab	Heart failure, demyelinating disorders, lupus-like syndrome Hepatic events especially with infliximab; no recommendations to monitor liver tests	Established mainstay of therapy. 30%–40% of patients are primary or secondary nonresponders. Certolizumab failed to induce remission of active CD in clinical trials[9,10]

Drug	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
Vedolizumab	Yes	Alternative to TNFIs	1st-line	Conditionally recommended for induction and maintenance Efficacy may be reduced when used after TNFIs.	Purportedly has lower risks of serious infection, malignancy, and immunogenicity than TNFIs; useful in elderly	Relatively gut selective; ineffective for extraintestinal involvement May be preferable over ustekinumab in patients who are older, have colonic CD, or have a history of cancer
Ustekinumab	No	Alternative to TNFIs	1st-line	Recommended for induction and maintenance NSD between ustekinumab and adalimumab in achieving and maintaining clinical remission[11]	Purportedly has lower risks of serious infection, malignancy, and immunogenicity than TNFIs	May be preferable over vedolizumab in patients who have psoriasis or psoriatic arthritis, require a faster onset (3 weeks vs 10 weeks), or refuse in-clinic IV maintenance infusions

CFU, Criteria for Use

Projected Place in Therapy

- **Epidemiology and Prevalence of Crohn's Disease**. From 1990 to 2016, the incidence of Crohn's disease remained stable or decreased in Western countries while it increased in developing countries in Africa, Asia, and South America. In North America the incidence and prevalence of Crohn's disease was estimated to be ≥ 6.38 per 100,000 person-years and >135.6 per 100,000, respectively.[12]
- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials were available, moderate-quality evidence from a network meta-analysis suggested that risankizumab-rzaa is better than vedolizumab in achieving clinical remission in patients with moderate to severe, active CD who have prior biologic exposure (i.e., for second-line therapy). The results of the network meta-analysis showed no significant differences in efficacy between risankizumab-rzaa and ustekinumab, an anti-IL-12/23 monoclonal antibody with less specific anti-IL-23 activity than risankizumab-rzaa. Moderate- to high-quality evidence from placebo-controlled trials supports the use of risankizumab-rzaa (with or without lower-dose corticosteroids and/or conventional immunomodulators) as induction and maintenance therapy in patients with moderate to severe, active CD who have had an inadequate response or intolerance to conventional therapies and/or other biologics. Although the higher maintenance dose (360 mg) seemed to provide little if any gain in CDAI clinical remission or endoscopic response efficacy over the lower dose (180 mg), it significantly improved clinical remission based on stool frequency and abdominal pain whereas the lower dose show no benefit. Overall, clinical remission and endoscopic response benefits were mostly moderate and were clinically meaningful. Hospitalization rates were not reported; however, risankizumab-rzaa numerically reduced the rates of serious adverse events relative to placebo. Risankizumab-rzaa may be effective for skin and joint comorbidities of CD based on its FDA approvals for plaque psoriasis and psoriatic arthritis. The efficacy and safety of risankizumab-rzaa was not reported in patients with fistulizing CD and not evaluated in patients with stricturing CD. The comparative efficacy and safety of combination therapy (with conventional immunomodulators) relative to risankizumab-rzaa monotherapy is unknown.
- **Potential Place in Therapy in VHA**. Based on drug cost and likely benefits, risankizumab-rzaa may be less preferred than TNFIs (infliximab-abda or adalimumab) as first-line treatment to induce clinical remission in patients with moderate to severe, active luminal CD who have an inadequate response

to conventional therapies. Based on moderate evidence of better efficacy, risankizumab-rzaa may be preferred over vedolizumab for second-line induction therapy in biologic-exposed patients. Unlike other biologics used for CD, risankizumab-rzaa has recommendations to monitor liver enzymes and bilirubin. Other treatments should be considered for patients with liver cirrhosis. The On-Body Injector, used only for the CD indication, will require patient education and may not be suitable for some patients (e.g., those who are blind without sighted assistance or have impaired dexterity).

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