Etrasimod (VELSIPITY) in Ulcerative Colitis

National Drug Monograph

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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 per 1000; AE, adverse event; AVB, atrioventricular block; CFB, change from baseline; CI, confidence interval; DB, double-blind; Diff, difference; EI, endoscopic improvement; GC, glucocorticoid; HistoR, histologic remission; INT, intolerance; IR, inadequate response; JAKi, Janus kinase inhibitor; LOR, loss of response; LSM, least squares mean; MMS, modified Mayo score; MN, multinational; OI, opportunistic infection; OLE, open-label extension; PC, placebo-controlled; PEM, Primary efficacy measure; RCT, randomized clinical trial; S1P, sphingosine 1-phosphate; TNFI, tumor necrosis factor inhibitor; UC, ulcerative colitis

FDA APPROVAL INFORMATION

Description / MOA	Etrasimod is a small molecule, sphingosine 1-phosphate (S1P) receptor modulator with high affinity to S1P receptors 1, 4, and 5. It inhibits egression of lymphocytes from lymphoid organs and reduces peripheral blood lymphocytes. In ulcerative colitis (UC), it may reduce lymphocyte migration into the intestines. It is the second S1P receptor modulator approved for UC. Ozanimod, the first S1P receptor modulator for UC, primarily binds to S1P receptors 1 and 5 with minimal or no activity on S1P receptors 2, 3 and 4.
Indication*	Treatment of moderately to severely active UC in adults.
Dosage Regimen[1]	**Pretreatment assessments are required**: Complete blood count; cardiac evaluation including electrocardiogram (ECG); liver function tests within the previous 6 months (transaminase and bilirubin levels); ophthalmic assessment in patients with a history of uveitis or macular edema; current or prior medications; vaccinations including varicella zoster virus (VZV) vaccination of antibody-negative patients and administration of any required live attenuated vaccines at least 4 weeks prior to initiating etrasimod; and skin examination. **Recommended dose**: 2 mg orally once daily. Swallow tablets whole with or without food. *PBM Note: Unlike ozanimod, initiation of etrasimod does not require up-titration.*
Dosage Form*	Tablets: 2 mg

* Under review

EFFICACY CONSIDERATIONS

Trial	**OASIS**[2] and 36-week OLE	**ELEVATE UC 12**[3]
Design	Proof-of-concept, phase 2 MN DB PC RCT; induction efficacy and safety. Randomization was stratified by GC use and prior TNFI exposure. PEM: CFB in MMS at Week 12 (clinical improvement) with etrasimod 2 mg vs placebo.	Phase 3 MN DB PC RCT; induction efficacy and safety. 2:1 randomization was stratified by prior exposure to biologics of JAKis (yes vs no), baseline GC use (yes vs no), and baseline disease activity (MMS of 4–6 vs 7–9) 12-week induction, 4-week follow-up, eligibility to enter an up to 5-year OLE PEM Analysis Population: Patients with MMS 5–9. PEM: Clinical remission at Week 12. Clinical remission was defined as a composite of stool frequency subscore of 0 (or stool frequency subscore of 1 with a ≥ 1-point decrease from baseline), rectal bleeding subscore of 0, and endoscopic subscore of ≤ 1 (without friability). EI–HistoR (Mucosal Healing) was defined as endoscopic subscore ≤1 without friability with histological remission (Geboes Index score < 2.0).
Population	156 adults with moderate to severe, active UC; MMS of 4–9 including endoscopic	354 adults with endoscopically confirmed moderate to severe, active UC and documented history of inadequate response, loss of response, or intolerance to at least one therapy approved for the treatment of UC (i.e., conventional therapies, TNFis, vedolizumab, ustekinumab, and tofacitinib). Patients with

	subscore of ≥ 2 and rectal bleeding subscore of ≥ 1. Stable doses of oral mesalamine and GC (prednisone ≤ 10 mg/d, budesonide ≤ 9 mg/d, or equivalent) were allowed. Excluded disease solely limited to the rectum. Baseline Characteristics: Age 42.8 y, male 57%, White 94.9%, prior TNFI 32%, prior anti-integrin 14.6%.	isolated proctitis were eligible if other entry criteria were met (maximum 15% of study population). Stable doses of aminosalicylates or GC (prednisone ≤ 20 mg/d, budesonide ≤ 9 mg/d, or equivalent) were allowed. Major Exclusions: Prior treatment with ≥ 3 biologics or ≥ 2 biologics plus a JAKi approved for UC; high risk of requiring colectomy in the next 3 months; clinically relevant cardiac condition (h/o MI, stroke, or 2nd–3rd-degree AVB); h/o OI or macular edema Baseline Characteristics: Age 40.4 y, male 60%, White 75%, Asian 21%, prior biologic or JAKi exposure 37% (mostly TNFIs 25%), concomitant GC at baseline 33%.
Intervention	Etrasimod 1 mg QD (N = 52) Etrasimod 2 mg QD (N = 50)	Etrasimod 2 mg QD (N = 238)
Comparator	Placebo (N = 54)	Placebo (N = 116)

Results

Efficacy outcomes at 12 weeks

Outcome	Etrasimod 2 mg	Placebo
CFB in MMS	2.49	1.50
Diff	0.99	
90% CI	0.30, 1.68	
P-value	0.009	
EI, n/N (%)	21/50 (41.8)	10/54 (17.8)
Diff	24.4	
90% CI	9.8, 39.0	

Etrasimod 1 mg was NSD from placebo in CFB in MMS and EI rate.

Exploratory Measures

Etrasimod vs placebo, respectively (all p-values are nominal):

- Clinical remission 33.0% vs 8.1% (P < 0.001)
- Clinical response 50.6% vs 32.5% (P = 0.03)
- Histologic remission 19.5% vs 6.1% (P = 0.03)

Key efficacy outcomes at 12 weeks

Outcome	Etrasimod 2 mg, n/N (%)	Placebo, n/N (%)	RR (95% CI)	AAE (95% CI)	Q
Clinical remission	55/222 (25)	17/112 (15)	1.6 (1.00, 2.68)	97 (11, 182)	L[αβ]
EI	68/222 (31)	21/112 (19)	1.6 (1.06, 2.52)	121 (30, 212)	L[αβ]
EI–HistoR	36/222 (16)	10/112 (9)	1.8 (0.94, 3.52)	74 (5, 144)	M[β]

[α] Downgraded for indirectness (estimate of endoscopic or histologic remission)

[β] Downgraded for imprecision (optimal information size not met)

Onset of effects: Week 4 based on first statistically significant treatment difference in symptomatic remission; Week 2 based on improvements in rectal bleeding and stool frequency subscores.

Trial	**ELEVATE UC 52**[3]
Design	Phase 3 MN DB PC RCT (2:1) with treat-through continuation period. 12-week induction + 40-week maintenance. Randomization was stratified by prior biologics or JAKi (yes vs no), baseline GC use (yes vs no), and baseline disease activity (MMS 4–6 vs 7–9). Co-PEMs: Clinical remission at Week 12 and at Week 52. Sustained clinical remission was defined as clinical remission at both Weeks 12 and 52.
Population	433 adults (16–80 y) with endoscopically confirmed moderate to severe, active UC, MMS of 4–9 including endoscopic subscore of ≥ 2 and rectal bleeding subscore of ≥ 1; IR, LOR or INT to ≥ 1 treatment approved for UC. Allowed isolated proctitis if other entry criteria were met (enrollment capped at 15%). Stable doses of GC (see doses used in OASIS) were allowed. GC doses had to be tapered after Week 12. Major Exclusions: Prior treatment with ≥ 3 biologics or ≥ 2 biologics + JAKi approved for UC; high risk of requiring a colectomy in the next 3 months; a clinically relevant cardiac condition (h/o MI, stroke, or 2nd- or 3rd-degree atrioventricular block); h/o OI or macular edema.
Intervention	Etrasimod 2 mg QD (N = 289)
Comparator	Placebo (N = 144)

Results

Key Efficacy Measures

Outcome	Etrasimod 2 mg n/N (%)	Placebo n/N (%)	RR (95% CI)	AAE (95% CI)	Q
Induction, Week 12					
Clinical remission	74/274 (27)	10/135 (7)	3.6 (1.95, 6.83)	198 (129, 266)	L[α,β]
EI	96/274 (35)	19/135 (14)	2.5 (1.59, 3.89)	212 (130, 293)	L[α,β]
EI–HistoR	58/274 (21)	6/135 (4)	4.8 (2.11, 10.76)	169 (108, 230)	M[β]
Continuation, Week 52					
Clinical remission	88/274 (32)	9/135 (7)	4.8 (2.50, 9.27)	254 (184, 324)	L[α,β]
EI	101/274 (37)‡	14/135 (10)‡	3.6 (2.11, 5.98)	267 (190, 344)	L[α,β]
EI–HistoR	71/274 (26)‡	11/135 (8)‡	3.2 (1.74, 5.80)	184 (114, 254)	M[β]
Sustained clinical remission	49/274 (18)	3/135 (2)	8.0 (2.55, 25.35)	158 (107, 210)	L[α,β]
CS-free remission†	88/274 (32)	9/135 (7)	4.8 (2.50, 9.27)	254 (184, 324)	L[α,β]

† No use of GC for ≥ 12 weeks among all patients regardless of baseline GC use. Similar results were seen among patients with documented GC use at baseline. All patients who achieved clinical remission were no longer taking CSs.
‡ Estimated from figure 3 in article.
[α] Downgraded for indirectness (estimate of endoscopic or histologic remission)
[β] Downgraded for imprecision (optimal information size not met)

Subgroup analyses: Etrasimod was statistically superior to placebo in biologic / JAKi–naïve and –experienced patients for all analyzed endpoints except not in biologic / JAKi–experienced patients in terms of symptomatic remission rates at Week 12 and Week 52. Biologic / JAKi–naïve patients had numerically greater treatment effects (differences between etrasimod and placebo) than biologic / JAKi–experienced patients at Week 52 for clinical remission (28.8% and 14.6%, respectively). Treatment effects were similar for EI (28.1% vs 23.1%) and EI-HistoR (18.7% vs 19.1%) for biologic / JAKi–naïve vs biologic / JAKi–experienced, respectively.

Limitations

Lack of responder re-randomization to assess efficacy of maintenance therapy. Lack of long-term safety experience beyond 1 year.

SAFETY CONSIDERATIONS

Boxed Warnings

None

Contraindications

- In the last 6 months, experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure.
- History or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker.

PBM Note: In contrast to ozanimod, etrasimod lacks contraindications for severe untreated sleep apnea and concomitant use of a monoamine oxidase (MAO) inhibitor.

Other Warnings

Infections and reduction in lymphocyte counts (serious and fatal infections have been reported with other S1PRMs); avoidance of live attenuated vaccines (during and for up to 5 weeks after treatment); bradyarrhythmias and atrioventricular conduction delays; liver injury; macular edema; increased blood pressure; fetal risk; malignancies; posterior reversible encephalopathy syndrome (PRES); respiratory effects (reductions in pulmonary function / forced expiratory volume over 1 second)[4]; unintended additive immune system effects from prior treatment with immunosuppressive or immunomodulators; immune system effects after stopping etrasimod (monitor for infections up to 5 weeks after the last dose if using concomitant immunosuppressants).

Top 5 AEs

Headache, elevated liver tests, dizziness, arthralgia, hypertension in 52-week study.

Headache, elevated liver tests, nausea, bradycardia, urinary tract infections in two 12-week studies.

AE of Interest

Decrease in visual acuity: 2.6% (4/156) on etrasimod vs 0% placebo in 52-week study.

Hepatic Impairment

Not recommended in severe hepatic impairment (Child-Pugh C).

No dosage adjustment is needed in mild to moderate hepatic impairment (Child-Pugh A and B).

Drug Interactions

Class Ia antiarrhythmics (e.g., quinidine, procainamide), Class III antiarrhythmics (e.g., amiodarone, sotalol), or other drugs that prolong the QT interval: Consult cardiologist before initiating etrasimod.

Beta-blockers or calcium channel blockers: Consult cardiologist before initiating a beta blocker or with concomitant use of other drugs that may decrease heart rate such as calcium channel blockers. Etrasimod may be started if beta blocker dose is stable.

		Antineoplastic, immunomodulating, or noncorticosteroid immunosuppressive therapies: Avoid concomitant use during and in the weeks following etrasimod therapy. Consider the half-life and mode of action of drugs to avoid unintended additive immunosuppression. **Moderate to strong inhibitor of CYP2C9 and CYP3A4**: Concomitant use of a drug that is a moderate to strong inhibitor of CYP2C9 and a moderate to strong inhibitor of CYP3A4 (e.g., fluconazole) is not recommended. **CYP2C9 poor metabolizers using moderate to strong inhibitors of CYP2C8 or CYP3A4**: Use is not recommended. **Rifampin**: Use is not recommended. *PBM Note: In contrast to ozanimod, which has an active metabolite that inhibits monoamine oxidase (MAO)-B in vitro, etrasimod does not interact with adrenergic and serotonergic drugs, tyramine, and MAO inhibitors..*
	FDA Safety Comments[4]	Bradyarrythmias, atrioventricular conduction delays, macular edema, fetal risk, and respiratory effects are unique to the S1P receptor modulators among drugs approved for the treatment of UC.

OTHER	**Onset of Effects**	Week 2 based on first statistically significant treatment difference in improvements in rectal bleeding and stool frequency subscores. The induction period lasted to Week 12. Symptomatic remission was achieved by 40% of patients by Week 12 and reached a peak of about 45% by Week 24.[3] It would seem reasonable to reassess and consider other treatment options if there has been no response to etrasimod by Week 12.
	Peak Effects	**Duration of an adequate therapeutic trial**: 24 weeks based on symptomatic remission rates over 48 weeks.
	Half-life	The elimination half-life of etrasimod is about 30 hours, compared with 21 hours for ozanimod and 11 days for the active ozanimod metabolite CC1084037.

PLACE IN THERAPY

DRUG	VANF	CFU / Other CG	FDA Place in Therapy in UC	2020 AGA Guideline Place in Therapy (2020)[5]	2019 ACG Guideline Place in Therapy (2019)[6]
S1PRMs					
Etrasimod	TBD	TBD	No prior treatments specified	Not mentioned (FDA-approved in 2023)	
Ozanimod	NonF	None / 3L*	No prior treatments specified	Not mentioned (FDA-approved in 2021)	
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	*Induction*: Recommended (in combination with a thiopurine) *Maintenance*: Recommended
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.	*Induction*: Recommended *Maintenance*: Recommended
Adalimumab / Biosimilar	PA-F,* -hwwd biosimilar is the preferred adalimumab product	—	No prerequisite therapy specified	*Induction, Biologic-naïve*: Alternative to infliximab (e.g., hypersensitivity) or vedolizumab	*Induction*: Recommended *Maintenance*: Recommended
Intregrin Receptor Antagonist					
Vedolizumab inj for IV use	PA-F	After TNFi or infliximab / BSM therapy	No prerequisite therapy specified	*Induction, Biologic-naïve*: Suggested over adalimumab	*Induction*: Recommended including in patients who previously failed TNFi therapy *Maintenance*: Recommended
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 specified	*Induction, Infliximab-exposed (particularly for PNR)*: Suggested over vedolizumab or adalimumab	Not mentioned; FDA-approved in 2019

	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	*Induction*: Recommended at dosage of 10 mg orally twice daily for 8 wks, including in patients who previously failed TNFi therapy *Maintenance*: Recommended
	Upadacitinib	NonF	Same as for tofacitinib	IR or INT to ≥ 1 TNFi	Not mentioned; FDA-approved in 2022	
	IL-23i					
	Mirikizumab-mrkz	TBD	TBD	No prerequisite therapy specified	Not mentioned; FDA-approved in 2023	

* The monograph Potential Place in Therapy puts ozanimod after trials of infliximab and vedolizumab.
CG, PBM clinical guidance

POTENTIAL USE

Potential Use in VHA

1. There were no active-controlled trials to inform the place in therapy of etrasimod. Etrasimod showed at least small benefits in achieving and sustaining clinical remission and endoscopic improvement in patients with moderate to severe active UC (low to moderate certainty evidence).
2. Potential advantages over ozanimod include lack of contraindications for severe untreated sleep apnea and concomitant monoamine oxidase inhibitor therapy; lack of a need to up-titrate initial doses; lack of a need to reinitiate therapy if a dose is missed in the first 2 weeks; lack of a need for dosage reduction in mild or moderate hepatic impairment (both drugs are not recommended in severe hepatic impairment); shorter duration of time to avoid live vaccinations after discontinuation of etrasimod (5 weeks) than ozanimod (3 months); and lower maintenance cost. Disadvantages of etrasimod vs ozanimod include CYP2C9 and CYP3A4 drug interactions.
3. For induction and maintenance of clinical remission in adults with moderately to severely active UC, etrasimod may be used in patients who have an intolerance or inadequate response to trials of infliximab and vedolizumab or for whom these treatments are medically inadvisable. Decisions to use etrasimod should take into consideration its significant safety concerns (mainly infections, bradyarrhythmias, and atrioventricular conduction delays).
4. Follow the FDA prescribing information for etrasimod to ensure appropriate use.

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