Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Velsipity®
Common Name: etrasimod
PDL Category: Anti-Inflammatories Non-NSAID

Comparable Products	Preferred Drug List Status
Humira	Preferred with Conditions
Zeposia	Non-Preferred with Conditions

Pharmacology/Usage: Etrasimod, the active ingredient of Velsipity®, is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1, 4, and 5. It partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood. The mechanism of action by which etrasimod exerts its therapeutic effects for its approved indication is not known, but may involve the reduction of lymphocyte migration into the intestines.

Indication: For the treatment of moderately to severely active ulcerative colitis (UC) in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies, Velsipity® may cause fetal harm when administered to pregnant women. Available data from reports of pregnancies from the clinical development program with Velsipity® are not sufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with increased disease activity in women with inflammatory bowel disease during pregnancy. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Velsipity® during pregnancy. Pregnant females exposed to Velsipity® and healthcare providers are encouraged to contact the registry by calling 1-800-616-3791. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 2mg.

Recommended Dosage: Before initiation of treatment with Velsipity®, assess the following:

- Obtain a recent complete blood count, including lymphocyte count.
- Obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist should be sought.
- Obtain recent transaminase and bilirubin levels.
- Obtain a baseline evaluation of the fundus, including the macula, near the start of treatment.
- Assess current or prior medications:
    - Determine if patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction.
    - If patients are taking anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before starting Velsipity® treatment.
- Patients without a healthcare professional-confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for

antibodies to VZV before starting Velsipity®; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Velsipity®.
    - If live *attenuated* vaccine immunizations are required, administer at least 4 weeks prior to initiation of Velsipity®. Avoid the use of live attenuated vaccines during and for 5 weeks after Velsipity®.
    - Update immunizations in agreement with current immunization guidelines prior to starting Velsipity®.
- Obtain a skin examination prior to or shortly after initiation of Velsipity®. If a suspicious skin lesion is observed, it should be promptly evaluated.

Take 2mg PO QD. Swallow whole, with or without food. Dosage adjustment is not required with mild to moderate hepatic impairment; however, use in patients with severe hepatic impairment is not recommended.

Increased exposure of etrasimod in patients who are CYP2C9 poor metabolizers is expected with concomitant use of moderate to strong inhibitors of CYP2C8 or CYP3A4. Concomitant use of Velsipity® is not recommended in these patients.

Drug Interactions: Etrasimod is mainly metabolized by CYP2C8, CYP2C9, and CYP3A4. The following includes drugs with clinically important drug interactions when administered concomitantly with Velsipity®.

The effect of concomitant use of Velsipity® with a combination of separate drugs that are moderate to strong inhibitors or inducers of either CYP2C8, CYP2C9, or CYP3A4 is unknown. However, a similar clinically significant change in exposure cannot be ruled out when two or more metabolic pathways are affected.

A transient decrease in heart rate and AV conduction delays may occur when starting Velsipity®. Because of the potential additive effect on heart rate, Velsipity® may increase the risk of QT prolongation and Torsade de Pointes with concomitant use of Class Ia and Class III anti-arrhythmic drugs and QT prolonging drugs. Obtain the advice of a cardiologist before starting Velsipity® treatment with Class Ia or Class III anti-arrhythmic drugs, or other drugs that prolong the QT interval.

Concomitant use of Velsipity® in patients receiving stable beta blocker treatment did not result in additive effects on heart rate reduction; however, the risk of additive heart rate reduction following the start of beta-blocker therapy with stable Velsipity® treatment or concomitant use with other drugs that may decrease heart rate is not known. Velsipity® can be initiated in patients receiving stable doses of beta blocker treatment. Obtain the advice of a cardiologist before starting a beta-blocker in a patient receiving stable Velsipity® or concomitant use with other drugs that may decrease heart rate (e.g., CCBs).

Velsipity® has not been studied in combination with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies. Avoid the concomitant use during and in weeks following administration of Velsipity®. When switching from drugs with prolonged immune effects, consider the half-life and mode of action of these drugs to avoid unintended additive immunosuppressive effects.

Concomitant use of Velsipity® with a drug that is a moderate to strong inhibitor of CYP2C9 and a moderate to strong inhibitor of CYP3A4 is not recommended.

Concomitant use of Velsipity® in patients who are CYP2C9 poor metabolizers using a moderate to strong inhibitor of CYP2C8 or CYP3A4 is not recommended.

Concomitant use of Velsipity® with rifampin is not recommended.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Velsipity®) minus reported % incidence for placebo in study UC-1. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (4%), elevated liver tests (1%), dizziness (3%), arthralgia (2%), hypertension (2%), urinary tract infection (1%), nausea (2%), hypercholesterolemia (3%), and herpes viral infection (1%). In this same study, for subjects with a baseline and follow-

up exam, a decrease in visual acuity was reported in 2.6% of subjects who received Velsipity® as compared with no subjects who received placebo.

Velsipity® causes a mean reduction in peripheral blood lymphocyte count to approximately 45% of baseline values at week 52 because of reversible sequestration of lymphocytes in lymphoid tissues. Thus, Velsipity® may increase the susceptibility to infections. Life-threatening and rare fatal infections have been reported in association with other S1P receptor modulators. Before starting treatment, obtain a recent complete blood count, including lymphocyte count. Delay the start of Velsipity® in patients with an active infection until the infection has resolved. Consider interruption of Velsipity® treatment if a patient develops a serious infection. In addition, progressive multifocal leukoencephalopathy (PML) has been reported in multiple sclerosis patients treated with S1P receptor modulators. If PML is suspected, Velsipity® treatment should be suspended until PML has been excluded by an appropriate diagnostic evaluation. If PML is confirmed, discontinue treatment with Velsipity®.

Initiation of Velsipity® may result in a transient decrease in heart rate and AV conduction delays. If treatment with Velsipity® is considered, advice from a cardiologist should be sought for those individuals:

- With significant QT prolongation (QTcF ≥450msec in males, ≥470 msec in females).
- With arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs or QT prolonging drugs.
- With unstable ischemic heart disease, Class I or II heart failure, history of cardiac arrest, cerebrovascular disease, or uncontrolled hypertension.
- With resting heart rate of less than 50bpm.
- With history of symptomatic bradycardia, recurrent cardiogenic syncope, or severe untreated sleep apnea.
- With history of Mobitz type I second-degree AV block, unless the patient has a functioning pacemaker.

Elevations of aminotransferases may occur in patients receiving Velsipity®. Obtain transaminase and bilirubin levels, if not recently available. Obtain transaminases and bilirubin levels in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue Velsipity® if significant liver injury is confirmed.

S1P receptor modulators, including Velsipity®, have been associated with an increased risk of macular edema. Obtain a baseline evaluation of the fundus, including the macula, near the start of treatment with Velsipity®. Periodically conduct an evaluation of the fundus, including the macula, while on therapy and any time there is a change in vision. Macular edema over an extended period of time (i.e., 6 months) can lead to permanent visual loss. Consider discontinuing Velsipity® if macular edema develops.

In clinical trials, subjects treated with Velsipity® had an average increase of about 1 to 4mmHg in systolic blood pressure (SBP) and about 1 to 2mmHg in diastolic blood pressure (DBP) compared to <1.5mmHg and <1mmHg in subjects receiving placebo, respectively. Monitor blood pressure during treatment and manage appropriately.

Cases of malignancies (including skin malignancies) have been reported in patients treated with S1P receptor modulators. Skin examinations are recommended prior to or shortly after the initiation of treatment, and periodically thereafter for all patients, especially those with risk factors for skin cancer. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving S1P receptor modulators. If a patient develops any neurological or psychiatric symptoms/signs, any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurologic deterioration, the physician should schedule a complete physical and neurological examination and should consider an MRI. If PRES is suspected, discontinue Velsipity® treatment.

Reductions in absolute forced expiratory volume over 1 second (FEV1) were observed in subjects treated with Velsipity® as early as 3 months after the start of treatment. There is not sufficient information to determine the

reversibility of the decrease in FEV1 after drug discontinuation. Spirometric evaluation of respiratory function should be performed during therapy with Velsipity® if clinically indicated.

After discontinuing Velsipity®, lymphocyte counts returned to the normal range in 90% of subjects within 4 to 5 weeks of stopping treatment. Use of immunosuppressants during this period may lead to an additive effect on the immune system, and thus monitor patients receiving concomitant immunosuppressants for infectious complications up to 5 weeks after the last dose of Velsipity®.

Contraindications: In patients who:

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

Manufacturer: Pfizer Laboratories.

Analysis: The efficacy of Velsipity® was assessed in 2 randomized, double-blind, placebo-controlled studies (UC-1 and UC-2) in adults with moderately to severely active ulcerative colitis (UC) who had an inadequate response, loss of response, or intolerance to one or more of the following treatment options, including oral aminosalicylates, corticosteroids, thiopurines, Janus kinase (JAK) inhibitors, or biologic therapies (e.g., TNF blocker, anti-integrin, anti-IL12/23). In both studies, subjects were randomized to Velsipity® or placebo and continued on treatment for the entire duration of the study, being 52 weeks with study UC-1 and 12 weeks with study UC-2.

Disease severity was assessed based on the modified Mayo score (mMS), a 3-component Mayo score (0 to 9) which consists of the following sub scores (0 to 3 for each sub score): stool frequency (SF), rectal bleeding (RB), and findings on centrally read endoscopy score (ES). An ES of 2 was defined by marked erythema, lack of vascular pattern, any friability, and/or erosions, and a score of 3 was defined by spontaneous bleeding and ulceration.

Subjects in these studies may have received other concomitant UC therapies, including stable daily doses of oral aminosalicylates and/or oral corticosteroids (≤20mg/day prednisone, ≤9mg/day budesonide, or equivalent steroid). Concomitant treatment with immunomodulators (e.g., thiopurines, methotrexate), biologic therapies, JAK inhibitors, rectal 5-ASA, or rectal corticosteroids was not permitted.

In the UC-1 study, efficacy was assessed in adults (N=408) with a baseline mMS of 5 to 9 (median of 7), including a centrally read endoscopy sub score of 2 or 3, and who were randomized to receive Velsipity® 2mg PO QD or placebo PO QD. Included subjects had a mean age of 41 years (range 18 to 78 years), while 45% were female, 89% were white, 30% had prior exposure to biologic/JAK inhibitors, and a total of 14% of subjects had exposure to >1 biologic/JAK inhibitor. At baseline, 68% of subjects were receiving oral aminosalicylates and 31% of subjects were receiving oral corticosteroids.

The co-primary endpoints were the proportion of subjects achieving clinical remission at week 12 and at week 52. The secondary endpoints included the proportion of subjects achieving endoscopic improvement, histologic-endoscopic mucosal improvement, corticosteroid-free clinical remission, and maintenance of clinical remission. Results are presented in the table below, which was adapted from the prescribing information.

Endpoints	Placebo	Velsipity®	Treatment difference
Co-primary Endpoints			
Clinical Remission at week 12			
Total Population	N=134 7%	N=274 27%	20% * (NNT = 5)
No prior biologic/JAK inhibitor exposure	N=93 10%	N=194 31%	

Endpoints	Placebo	Velsipity®	Treatment difference
Prior biologic/JAK inhibitor exposure	N=41 2%	N=80 18%	
Clinical Remission at week 52			
Total Population	N=134 7%	N=274 32%	26% * (NNT = 4)
No prior biologic/JAK inhibitor exposure	N=93 8%	N=194 37%	
Prior biologic/JAK inhibitor exposure	N=41 5%	N=80 21%	
Week 12 Endpoints			
Endoscopic Improvement			
Total Population	N=134 14%	N=274 35%	21% * (NNT = 5)
No prior biologic/JAK inhibitor exposure	N=93 18%	N=194 39%	
Prior biologic/JAK inhibitor exposure	N=41 5%	N=80 25%	
Histologic-Endoscopic Mucosal Improvement			
Total Population	N-134 4%	N=274 21%	17% * (NNT = 6)
No prior biologic/JAK inhibitor exposure	N=93 6%	N=194 24%	
Prior biologic/JAK inhibitor exposure	N=41 0%	N=80 14%	
Week 52 endpoints			
Endoscopic Improvement			
Total Population	N=134 10%	N=274 37%	27% * (NNT = 4)
No prior biologic/JAK inhibitor exposure	N=93 13%	N=194 40%	
Prior biologic/JAK inhibitor exposure	N=41 5%	N=80 30%	
Histologic-Endoscopic Mucosal Improvement			
Total Population	N=134 8%	N=274 27%	18% * (NNT = 6)
No prior biologic/JAK inhibitor exposure	N=93 11%	N=194 28%	
Prior biologic/JAK inhibitor exposure	N=41 2%	N=80 23%	
Corticosteroid-Free Clinical Remission			

Endpoints	Placebo	Velsipity®	Treatment difference
Total Population	N=134 7%	N=274 32%	26% * (NNT = 4)
No prior biologic/JAK inhibitor exposure	N=93 8%	N=194 37%	
Prior biologic/JAK inhibitor exposure	N=41 5%	N=80 21%	
Maintenance of Clinical Remission			
Total Population	N=134 2%	N=274 18%	16% * (NNT = 7)
No prior biologic/JAK inhibitor exposure	N=93 2%	N=194 22%	
Prior biologic/JAK inhibitor exposure	N=41 2%	N=80 10%	

* $p<0.001$

The relationship of histologic-endoscopic mucosal improvement at week 12 or week 52 to disease progression and longer-term outcomes after week 52 was not evaluated in study UC-1.

Regarding clinical response, a greater proportion of subjects treated with Velsipity® compared to placebo achieved clinical response, defined as a ≥2 point and ≥30% decrease from baseline in mMS, and a ≥1 point decrease from baseline in RB sub score or an absolute RB sub score ≤1 at week 12 (62% vs 34%).

Regarding stool frequency and rectal bleeding sub scores, decreases in SF sub scores were observed as early as week 2 and decreases in RB sub scores were observed as early as week 4 in subjects treated with Velsipity® compared to placebo.

Regarding endoscopic assessment, normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. A greater proportion of subjects treated with Velsipity® compared to placebo achieved endoscopic remission by week 12 (15% vs 4%), week 52 (26% vs 6%), and both week 12 and week 52 (11% vs 1%).

In the UC-2 study, efficacy was assessed in adults (N=333) with a baseline of mMS of 5 to 9 (median of 7), including a centrally read endoscopy sub score of 2 or 3, who were randomized to receive Velsipity® 2mg or placebo both administered PO QD. Included subjects had a mean age of 41 years (range 18 to 73), 41% were female, 76% were white, 34% had prior exposure to biologic/JAK inhibitors, and a total of 17% had exposure to >1 biologic/JAK inhibitor. At baseline, 66% of subjects were receiving oral aminosalicylates and 28% were receiving oral corticosteroids.

The primary endpoint was the proportion of subjects achieving clinical remission at week 12. The secondary endpoints included the proportion of subjects achieving endoscopic improvement and histologic-endoscopic mucosal improvement at week 12. Results are presented in the table below, which was adapted from the prescribing information.

Endpoints	Placebo	Velsipity®	Treatment difference
Clinical Remission			
Total Population	N=112 15%	N=221 26%	11% * (NNT = 10)
No prior biologic/JAK inhibitor exposure	N=74 16%	N=147 30%	

Endpoints	Placebo	Velsipity®	Treatment difference
Prior biologic/JAK inhibitor exposure	N=38 13%	N=74 19%	
Endoscopic Improvement			
Total Population	N=112 19%	N=221 30%	12% * (NNT = 9)
No prior biologic/JAK inhibitor exposure	N=74 19%	N=147 34%	
Prior biologic/JAK inhibitor exposure	N=38 18%	N=74 23%	
Histologic-Endoscopic Mucosal Improvement			
Total Population	N=112 9%	N=221 16%	8% * (NNT = 13)
No prior biologic/JAK inhibitor exposure	N=74 11%	N=147 19%	
Prior biologic/JAK inhibitor exposure	N=38 5%	N=74 11%	

*p<0.05

The relationship of histologic-endoscopic mucosal improvement at week 12 to disease progression and longer-term outcomes after week 12 was not assessed in study UC-2.

Regarding clinical response, a greater proportion of subjects treated with Velsipity® compared to placebo achieved clinical response, defined as a ≥2 point and ≥30% decrease from baseline in mMS, and a ≥1 point decrease from baseline in RB sub score or an absolute RB sub score ≤1 at week 12 (62% vs 41%).

Regarding stool frequency and rectal bleeding sub scores, decreases in SF sub scores were observed as early as week 2 and decreases in RB sub scores were observed as early as week 4 in subjects treated with Velsipity® compared to placebo.

Regarding endoscopic assessment, normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. A greater proportion of subjects treated with Velsipity® compared to placebo achieved endoscopic remission by week 12 (17% vs 8%).

Place in Therapy: Velsipity®, a sphingosine 1-phosphate (S1P) receptor modulator, is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults. Before initiation of treatment with Velsipity®, obtain a recent complete blood count, an electrocardiogram (ECG, to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist should be sought.), obtain recent transaminase and bilirubin levels, and obtain a baseline evaluation of the fundus, including the macula. Review current or prior medications. In addition, obtain a skin exam prior to or shortly after initiation of Velsipity®. Varicella zoster virus (VZV) vaccination of antibody-negative patients is recommended prior to starting treatment.

Two randomized, double-blind, placebo-controlled, phase 3 studies assessed the safety and efficacy of Velsipity® as compared with placebo in adults with moderately to severely active UC who had an inadequate response, loss of response, or intolerance to one or more of the following treatment options, including oral aminosalicylates, corticosteroids, thiopurines, Janus kinase inhibitors, or biologic therapies. The co-primary endpoints of Study 1 were the proportion of subjects achieving clinical remission at week 12 and at week 52. The primary endpoint of Study 2

was the proportion of subjects achieving clinical remission at week 12. Velsipity® was significantly more effective than placebo for the primary endpoints. Head-to-head comparator studies with other active ingredients were not currently found.

There is no evidence at this time to support that Velsipity® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Velsipity® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Velsipity® [package insert]. New York, NY: Pfizer Labs, Division of Pfizer Inc; 2023.