PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]VELSIPITY™

Etrasimod tablets

Tablet, 2 mg etrasimod (as etrasimod L-arginine), Oral

Selective Sphingosine 1-phosphate receptor modulator

Pfizer Canada ULC

17,300 Trans-Canada Highway

Kirkland, Quebec H9J 2M5

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VELSIPITY (etrasimod) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or an advanced treatment.

1.1 Pediatrics

Pediatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

There are limited data available on patients aged 65 years and older. No clinically significant differences in the pharmacokinetics of etrasimod were observed based on age (see **10.3 Pharmacokinetics**). No dose adjustment is needed in patients over 65 years of age. In general, use of VELSIPITY in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

2 CONTRAINDICATIONS

VELSIPITY is contraindicated in the following circumstances:

- In patients with hypersensitivity to the active substance or to any of the non-medicinal ingredients listed in **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** (see Table 1).
- In patients who, in the last 6 months, have experienced a myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or New York Heart Association (NYHA) Class III/IV heart failure.
- In patients with a history of or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker.
- In patients with increased risk of opportunistic infections, including those who are immunocompromised due to treatment (e.g., antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g., immunodeficiency syndrome) (see **7 WARNINGS AND PRECAUTIONS**).
- In patients with severe active infections, active chronic infections.
- In patients with active malignancies.
- During pregnancy and in women of childbearing potential not using effective contraception (see **7 WARNINGS AND PRECAUTIONS** and **7.1.1 Pregnant Women**).
- In breast-feeding women (see **7.1.2 Breast-Feeding**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Before initiation of treatment with VELSIPITY, assess the following:

Cardiac Evaluation
Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought (see **2 CONTRAINDICATIONS** and **7 WARNINGS AND PRECAUTIONS**).

Complete Blood Count
Obtain a recent complete blood count (CBC), including lymphocyte count (i.e., within the last 6 months or after discontinuation of prior UC therapy). See **7 WARNINGS AND PRECAUTIONS.**

Liver Function Tests
Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels (see **7 WARNINGS AND PRECAUTIONS**).

Ophthalmic Assessment
In patients with a history of diabetes mellitus, uveitis, or retinal disease, obtain an evaluation of the fundus, including the macula (see **7 WARNINGS AND PRECAUTIONS**)

Current or Prior Medications

- Determine if patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction (see **7 WARNINGS AND PRECAUTIONS**).
- 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 immune system effects before initiating treatment with VELSIPITY (see **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS** and **9.4 Drug-Drug Interactions**).

Vaccinations
Update immunizations in agreement with current immunization guidelines prior to initiating VELSIPITY therapy (see **7 WARNINGS AND PRECAUTIONS** and **9.4 Drug-Drug Interactions**).

If live *attenuated* vaccine immunizations are required, administer at least 4 weeks prior to initiation of VELSIPITY.

Pregnancy
Pregnancy must be excluded before start of treatment as VELSIPITY may cause fetal harm. Consult the patient about the risk of becoming pregnant while taking etrasimod (see **2 CONTRAINDICATIONS**, **7 WARNINGS AND PRECAUTIONS** and **7.1.1 Pregnant Women**).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of VELSIPITY is 2 mg taken once daily taken orally.

Special populations
Elderly
There are limited data available on patients aged 65 years and older. No clinically significant differences in the pharmacokinetics of etrasimod were observed based on age (**10.3 Pharmacokinetics**). No dose adjustment is needed in patients over 65 years of age. In general,

VELSIPITY in elderly patients should be used with caution, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal impairment
No dose adjustment is needed for patients with renal impairment (**10.3 Pharmacokinetics**).

Hepatic impairment
Use of VELSIPITY in patients with severe hepatic impairment is not recommended. No dosage adjustment is needed in patients with mild to moderate hepatic impairment. (**10.3 Pharmacokinetics**).

Pediatric population
The safety and efficacy of VELSIPITY in children and adolescents has not been established.

4.4 Administration

Oral use.

VELSIPITY should be swallowed whole and can be administered with or without food (see **10.3 Pharmacokinetics**).

First dose cardiac monitoring

Due to the risk of transient decreases in heart rate with the initiation of etrasimod, first dose, 4-hour monitoring for signs and symptoms of symptomatic bradycardia after the first dose is recommended in patients with resting heart rate < 50 bpm, first degree or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure.

Patients should be monitored with hourly pulse and blood pressure measurement during this 4- hour period. An ECG prior to and at the end of this 4- hour period is recommended.

Additional monitoring is recommended in patients, if at the end of 4- hour periods:

• Heart rate is < 45 bpm.

• Heart rate is the lowest value post dose, suggesting that the maximum decrease in heart rate may not have occurred yet.

• ECG shows evidence of a new onset second-degree or higher AV block.

• QTc interval is ≥ 500 msec.

In these cases, appropriate management should be initiated, and observation should continue until the symptoms/findings have resolved. If medical treatment is required, monitoring should be continued overnight, and a 4 -hour monitoring period should be repeated after the second dose of etrasimod (see section **10.2 Pharmacodymanic**).

4.5 Missed Dose

If a dose is missed, the patient should be advised to take the dose as soon as remembered. However, if a missed dose is forgotten for the whole day, the patient should skip the missed dose and take the next dose at the usual time. The patient should not double the dose to make up for a forgotten dose. Patients who miss a dose for 2 or more consecutive days within the first week of treatment or for more than seven consecutive days should contact their health care provider to discuss treatment re-initiation.

5 OVERDOSAGE

In patients with overdosage of etrasimod, monitor for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of heart rate, blood pressure, and ECGs should be performed. There is no specific antidote to etrasimod available. The decrease in heart rate induced by etrasimod can be reversed by parenteral atropine.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 2 mg etrasimod (as etrasimod L-arginine)	The core contains magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate. The green film coat contains FD&C blue #1/brilliant blue FCF aluminum lake, FD&C blue #2/indigo carmine aluminum lake, FD&C yellow #5/tartrazine aluminum lake, macrogol 4000 JP/PEG 3350, polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide.

Tablet: 2 mg VELSIPITY are green, round, film-coated tablets, debossed with “ETR” on one side and “2” on the other side.

Packaging

VELSIPITY is packaged in blister or bottle. Each blister pack contains 28 tablets (2x14 aluminum blister strips) or 98 tablets (7x14 aluminum blister strips). Each bottle will contain 30 tablets.

7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Malignancies

Cases of malignancies (including cutaneous malignancies) have been reported in patients treated with S1P receptor modulators. Skin examinations are recommended prior to or shortly after the start of treatment and periodically thereafter for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk 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.

Cardiovascular

Prior to treatment initiation with etrasimod, an electrocardiogram (ECG) in all patients should be obtained to assess for pre-existing cardiac abnormalities. Initiation of etrasimod may result in a transient decrease in heart rate and AV conduction delays (see **8 ADVERSE REACTIONS** and **10 CLINICAL PHARMACOLOGY**).

Decrease in heart rate

Transient decreases in heart rate were observed in healthy subjects and UC patients that were most pronounced following the first dose of 2 mg etrasimod. In UC patients, the largest mean decrease in heart rate occurred 2-3h post dose (see **10 CLINICAL PHARMACOLOGY**).
Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, such as dizziness, and these symptoms resolved without intervention.

AV Conduction Delays

PR interval prolongation was observed in healthy subjects and UC patients that was most pronounced following the first dose of 2mg etrasimod. This resulted in incidences of first- or second-degree Mobitz type I AV blocks in UC patients administered etrasimod that were not observed in patients administered placebo (see **8 ADVERSE REACTIONS** and **10 CLINICAL PHARMACOLOGY**).

If treatment with VELSIPITY is considered, advice from a cardiologist should be sought, for those individuals:

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

Driving and Operating Machinery

No studies on the effects on the ability to drive and the use of machines have been performed. However, patients who experience dizziness after taking etrasimod should refrain from driving or operating dangerous equipment until the dizziness resolves (see **8 ADVERSE REACTIONS**).

Hepatic/Biliary/Pancreatic

Liver injury: Elevations of aminotransferases may occur in patients receiving etrasimod (see **8 ADVERSE REACTIONS**). Recent (i.e., within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with etrasimod.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked and etrasimod should be discontinued if significant liver injury is confirmed.
Use of VELSIPITY in patients with severe hepatic impairment is not recommended. No dosage adjustment is needed in patients with mild to moderate hepatic impairment (see **7 WARNINGS AND PRECAUTIONS** and **10.3 Pharmacokinetics**).

Immune

Risk of infections: Etrasimod 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 (see **10 CLINICAL PHARMACOLOGY**). Etrasimod may, therefore, increase the susceptibility to infections (see **8 ADVERSE REACTIONS**).

Before initiating treatment, obtain a recent complete blood count (CBC), including lymphocyte count (i.e., within the last 6 months or after discontinuation of prior UC therapy).

The initiation of etrasimod in patients with any active infection should be delayed until the infection is resolved (see **2 CONTRAINDICATIONS**).

Consider interruption of treatment with VELSIPITY if a patient develops a serious infection.

Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist up to 5 weeks after discontinuation of etrasimod, vigilance for infection should be continued throughout this period (see **10 CLINICAL PHARMACOLOGY**). In 90% of subjects, peripheral blood absolute lymphocyte counts returned to normal range within 2 weeks of stopping therapy.

Progressive multifocal leukoencephalopathy (PML)
PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised, and that may lead to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No cases of PML have been reported in etrasimod-treated patients in the development program; however, PML has been reported in multiple sclerosis patients treated with other sphingosine 1-phosphate (S1P) receptor modulators and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or unexplained neurologic findings that may be suggestive of PML. If PML is suspected, treatment with etrasimod should be suspended until PML has been excluded by an appropriate diagnostic evaluation.

If PML is confirmed, treatment with etrasimod should be discontinued.

Herpes Viral Infection
In a 52 week pivotal UC clinical study, herpes zoster was reported in 0.7% of subjects treated with etrasimod, and none in subjects who received placebo. Herpes simplex encephalitis and varicella zoster meningitis have been reported with other S1P receptor modulators. Physicians should be vigilant for clinical symptoms that may be suggestive of serious herpetic infections.

Cryptococcal Infection
Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported with other S1P receptor modulators. Physicians should be vigilant for clinical symptoms or signs of CM. Patients with symptoms or signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment. Etrasimod treatment should be suspended until a

cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Prior and concomitant treatment with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies

In ELEVATE UC 52 and ELEVATE UC 12, patients who received etrasimod were not to receive concomitant treatment with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies used for the treatment of UC. In ELEVATE UC 52 and ELEVATE UC 12, concomitant use of corticosteroids was allowed and did not appear to influence the safety or efficacy of etrasimod (see **10 CLINICAL PHARMACOLOGY**).

VELSIPITY is contraindicated in patients with increased risk of opportunistic infections, including those who are immunocompromised due to treatment (e.g., antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g., immunodeficiency syndrome) immunodeficient state.

When switching to etrasimod from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immune system effects.

Immunizations: No clinical data are available on the safety and efficacy of vaccinations in patients taking etrasimod. Vaccinations may be less effective if administered during etrasimod treatment. If live attenuated vaccine immunizations are required, administer at least 4 weeks prior to initiation of etrasimod. Avoid the use of live attenuated vaccines during and for 2 weeks after treatment with etrasimod.

Update immunizations in agreement with current immunization guidelines prior to initiating VELSIPITY therapy.

Monitoring and Laboratory Tests

Increased blood pressure: In clinical studies, hypertension was more frequently reported in patients treated with etrasimod than in patients treated with placebo (see **8 ADVERSE REACTIONS**). Blood pressure should be monitored during treatment with etrasimod and managed appropriately.

Neurologic

Posterior reversible encephalopathy syndrome (PRES): Rare cases of PRES have been reported in patients receiving other S1P receptor modulators. Such events have not been reported for etrasimod-treated patients in the development program. Should an etrasimod-treated patient develop any neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioural changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with etrasimod should be discontinued.

Ophthalmologic

Macular oedema: In the ulcerative colitis clinical development program, there were 2 cases of macular oedema in subjects taking etrasimod 2 mg. An increased risk of macular oedema is known to be associated with S1P receptor modulators. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking etrasimod.

Patients with a history of diabetes mellitus, uveitis, or underlying/coexisting retinal disease, are at increased risk of macular oedema during etrasimod therapy (see **8 ADVERSE REACTIONS**). It is recommended that patients with a history of diabetes mellitus, uveitis, or retinal disease undergo an ophthalmic evaluation prior to treatment initiation with etrasimod and have follow up evaluations while receiving therapy.
Continuation of VELSIPITY therapy in patients who develop macular edema has not been evaluated. A decision on whether or not VELSIPITY should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Renal
No dose adjustment is needed for patients with renal impairment (see **10.3 Pharmacokinetics**).

Reproductive Health: Female and Male Potential
VELSIPITY is contraindicated in women who are pregnant or of childbearing potential not using effective contraception. Females of childbearing potential must use effective contraception (See **2 CONTRAINDICATIONS**, **7.1.1 Pregnant Women**).

- Fertility
  The effect of etrasimod on human fertility has not been evaluated. In animal studies, no adverse effects on fertility were observed (see **16 NON-CLINICAL TOXICOLOGY**).

- Teratogenic Risk
  There are no adequate and well-controlled studies in pregnant women. When etrasimod was orally administered to pregnant rats and rabbits during the period of organogenesis foetal visceral and or skeletal malformations and variations were observed. Maternal plasma AUC at the lowest dose tested in rats was approximately 5 times that in humans at the recommended human dose (RHD) of 2 mg per day and in rabbits, maternal plasma AUC at the no-adverse effect dose (2 mg/kg/day) was approximately 0.8 times that in humans of the RHD of 2 mg/day (see **7.1.1 Pregnant Women** and **16 NON-CLINICAL TOXICOLOGY**).

Respiratory

Respiratory effects: Reductions in absolute forced expiratory volume over 1 second (FEV_1) and forced vital capacity (FVC) were observed in patients treated with S1P receptor modulators, including etrasimod (see **10 CLINICAL PHARMACOLOGY**). Etrasimod should be used with caution in patients with severe respiratory disease (e.g., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease). Spirometric evaluation of respiratory function should be performed at baseline and during therapy with VELSIPITY if clinically indicated.

7.1 Special Populations

Women of childbearing potential: Before initiation of etrasimod treatment, women of childbearing potential should be counseled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with etrasimod (see **7.1.1 Pregnant Women**).

Because of the time it takes to eliminate the drug from the body after stopping treatment, the potential risk to the fetus may persist and women of childbearing potential should use effective contraception for 6 days after stopping etrasimod.

7.1.1 Pregnant Women

Etrasimod is contraindicated in women who are pregnant or of childbearing potential not using effective contraception. There are no adequate and well-controlled studies on the developmental risk associated with the use of etrasimod in pregnant women. Based on the data from animal reproductive and developmental toxicity studies and its mechanism of action, VELSIPITY may cause fetal harm when administered to a pregnant woman.

In animal studies, administration of etrasimod during pregnancy produced adverse effects on development, including embryolethality and fetal malformations, in both rats and rabbits at clinically relevant maternal exposures (see **16 NON-CLINICAL TOXICOLOGY**).

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to VELSIPITY during pregnancy. Pregnant females exposed to VELSIPITY and healthcare providers are encouraged to contact the pregnancy registry by calling 1-800-616-3791.

7.1.2 Breast-feeding

VELSIPITY is contraindicated in breast-feeding women. Although it is unknown whether etrasimod is excreted in human milk, when etrasimod was orally administered to female rats during pregnancy and lactation, etrasimod was detected in the plasma of the offspring, suggesting excretion of etrasimod in milk.

7.1.3 Pediatrics

Pediatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

There are limited data available on patients aged 65 years and older. No clinically significant differences in the pharmacokinetics of etrasimod were observed based on age (see **10.3 Pharmacokinetics**). No dose adjustment is needed in patients over 65 years of age. In general, use of VELSIPITY in elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of VELSIPITY was evaluated in 2 randomized, double-blind, placebo-controlled clinical studies (ELEVATE UC 52, n = 289; and ELEVATE UC 12, n = 238) in patients 16 to 80 years of age with mMS 4 to 9. Additional data from a phase 2 (12-week placebo-controlled) (OASIS UC) study included 50 patients who received VELSIPITY 2 mg once daily. Elevate UC 52-week study safety data and pooled safety data from 12 week studies (Elevate UC 12 and OASIS UC) are presented separately.

The most common adverse drug reactions are lymphopenia (11%) and headache (7%).

Bradyarrhythmia
In ELEVATE UC 52, bradycardia was reported on the day of treatment initiation in 3 (1.0%) patients treated with VELSIPITY compared to none in patients who received placebo. On Day 2, bradycardia was reported in 1 patient (0.3%) treated with VELSIPITY compared to none in patients who received placebo. In both UC 12 week studies, bradycardia was reported on the day of treatment initiation in 7 (2.4%) patients treated with VELSIPITY compared to none in patients who received placebo. On Day 2, bradycardia was reported in 1 patient (0.4%) treated with VELSIPITY compared to none in patients who received placebo.

At initiation of VELSIPITY 2 mg, events of first- or second-degree Mobitz type I AV blocks were observed in 2 (0.6%) VELSIPITY -treated patients compared to none in placebo in ELEVATE UC 52 and in 1 (0.4%) of VELSIPITY treated patient compared to none in placebo in pooled both UC 12 week studies. No events of second degree Mobitz type II AV block or higher AV block were reported in patients treated with VELSIPITY in any of these studies.

Infections
In ELEVATE UC 52, the overall rate of infections in subjects treated with VELSIPITY was 24.9% compared to 22.2% in subjects who received placebo. In both UC12 week studies, the overall rate of infections in subjects treated with VELSIPITY was 14.0% compared to 11.8% in subjects who received placebo. The most common infections were urinary tract infections, which were higher in VELSIPITY treated subjects.

Blood lymphocyte count reduction
The proportion of patients treated with VELSIPITY who experienced lymphocyte counts less than 0.2×10^9/L was 5.6% in ELEVATE UC 52 and 0.9% in UC 12 Week studies.

Elevated hepatic enzymes
In ELEVATE UC 52, elevations of ALT to 5-fold the ULN or greater occurred in 2 (0.7%) patients treated with VELSIPITY and 1 (0.7%) patients who received placebo, and in UC 12 week studies elevations of ALT to 5-fold the ULN or greater occurred in 2 (0.7%) patients treated with VELSIPITY and no patients who received placebo. In ELEVATE UC 52, elevations of ALT to 3-fold the ULN or greater occurred in 13 (4.5%) patients treated with VELSIPITY and 1 (0.7%) patient who received placebo, and in UC 12 week studies elevations of ALT to 3-fold the ULN or greater occurred in 6 (2.1%) patients treated with VELSIPITY and no patients who received placebo.

The majority (75%) of patients with ALT greater than 3-fold the ULN continued treatment with VELSIPITY with values returning to less than 3-fold the ULN while on treatment.

Increased blood pressure
In ELEVATE UC 52 and both UC-12 week studies, patients treated with VELSIPITY had an average increase of approximately 1 to 4 mm Hg in systolic blood pressure and approximately 1 to 2 mm Hg in diastolic blood pressure compared to < 1.5 mm Hg and < 1 mm Hg in patients receiving placebo, respectively. The increase was first detected after 2 weeks of treatment and remained within the specified average range in blood pressure increases throughout treatment. In ELEVATE UC 52, hypertension was reported as an adverse event in 9 (3.1%) patients treated with VELSIPITY and 1 (0.7%) patient who received placebo. In both UC 12 week studies, hypertension was reported as an adverse event in 5 (1.7%) patients treated with VELSIPITY and 2 (1.2%) patients who received placebo. The majority of hypertension events were mild or moderate in severity.

Macular oedema
In ELEVATE UC 52, macular oedema was reported in 1 patient (0.3%) treated with VELSIPITY and in no patients receiving placebo. In UC 12 week studies, macular oedema was reported in 1 patient (0.4%) treated with VELSIPITY and in 1 patient (0.9%) receiving placebo.

Herpes viral infections
Cases of localized herpes viral infection were seen with S1P receptor modulators, including VELSIPITY. In ELEVATE UC 52, herpes zoster was reported in 2 (0.7%) patients treated with VELSIPITY and in none of the patients who received placebo. In UC 12 week studies, herpes zoster was reported in none of the patients treated with VELSIPITY and in 2 (1.2%) patients who received placebo. In ELEVATE UC 52, oral herpes was reported in 2 (0.7%) patients treated with VELSIPITY and in 1 (0.7%) patient who received placebo. In UC 12 week studies, oral herpes was reported in 1 (0.3%) patient treated with VELSIPITY and in none of the patients who received placebo. In ELEVATE UC 52, herpes simplex was reported in 1 (0.3%) patient treated with VELSIPITY and in none of the patients who received placebo.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2: Treatment- Emergent Adverse Events Reported by ≥1% of Patients Treated with VELSIPITY and ≥1% higher than placebo- UC Phase 3 52-week Study

System Organ Class **Preferred Term**	Etrasimod 2 mg (N = 289) n (%)	Placebo (N = 144) n (%)
Cardiac disorders		
Bradycardia [a]	4 (1.4)	0
Gastrointestinal disorders		
Diarrhoea	5 (1.7)	1 (0.7)
Flatulence	6 (2.1)	0
Gastritis	3 (1.0)	0
Haemorrhoids	7 (2.4)	0
Nausea	9 (3.1)	2 (1.4)
Stomatitis	3 (1.0)	0

Vomiting	5 (1.7)	0
General disorders and administration site conditions		
Asthenia	7 (2.4)	2 (1.4)
Infections and infestations		
Bronchitis	3 (1.0)	0
Urinary tract infection[b]	10 (3.5)	3 (2.1)
Herpes viral infection [c]	5 (1.7)	1 (0.7)
Upper respiratory tract infection[d]	8 (2.8%)	1 (0.7%)
Investigations		
Elevated liver enzymes [e]	17 (5.9)	7 (4.9)
Blood creatine phosphokinase increased	5 (1.7)	1 (0.7)
Metabolism and nutrition disorders		
Hypercholesterolaemia[f]	8 (2.8)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (4.5)	3 (2.1)
Muscle spasms	5 (1.7)	0
Neck pain	3 (1.0)	0
Nervous system disorders		
Dizziness [g]	15 (5.2)	3 (2.1)
Headache [h]	27 (9.3)	7 (4.9)
Vascular disorders		
Hypertension [i]	9 (3.1)	1 (0.7)

Note: TEAEs are defined as any adverse event that started on or after the first dose of study treatment. Terms are coded using MedDRA v24.1. Percentages are based on the number of subjects in the analysis set. Adverse events are sorted by decreasing frequency of preferred term in the etrasimod treatment group. Subjects are counted only once per summarization level; [n] is defined as the number of events.

[a] Bradycardia includes bradycardia and sinus bradycardia

[b] Urinary tract infection includes urinary tract infection and cystitis

[c] Herpes viral infection includes herpes zoster, oral herpes and herpes simplex

[d] Upper respiratory tract infection includes pharyngitis, rhinorrhoea and sinusitis

[e] Elevated liver enzymes includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, blood alkaline phosphatase increased, cholestasis, hyperbilirubinaemia and liver function test increased

[f] Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased

[g] Dizziness includes dizziness, dizziness exertional and dizziness postural

[h] Headache includes headache, migraine and tension headache

[i] Hypertension includes hypertension and blood pressure increased

Table 3: Treatment- Emergent Adverse Events Reported by ≥1% of Patients Treated with VELSIPITY and ≥1% higher than placebo- UC 12-week Studies

System Organ Class **Preferred Term**	Etrasimod 2 mg (N = 288) n (%)	Placebo (N = 170) n (%)
Cardiovascular disorders		
Bradycardia[a]	7 (2.4)	0
Eye disorders		
Vision blurred	3 (1.0)	0
Gastrointestinal disorders		
Nausea	11 (3.8)	4 (2.4)
Abdominal distension	5 (1.7)	0
Diarrhoea	4 (1.4)	0
General disorders and administration site conditions		
Pyrexia	10 (3.5)	4 (2.4)
Hepatobiliary disorders		
Liver disorder	3 (1.0)	0
Infections and infestations		
Urinary tract infection[b]	7 (2.4)	0
Upper respiratory tract infection[c]	4 (1.4%)	0
Herpes viral infection [d]	1 (0.3)	2 (1.2)
Investigations		
Elevated liver enzymes [e]	11 (3.8)	1 (0.6)
Blood creatine phosphokinase increased	5 (1.7)	1 (0.6)
Metabolism and nutrition disorders		
Hypercholesterolaemia[f]	4 (1.4)	1 (0.6)
Hypophosphataemia	4 (1.4)	0
Musculoskeletal and connective tissue disorders		
Back pain	4 (1.4)	0
Nervous system disorders		
Dizziness [g]	4 (1.4)	1 (0.6)
Headache [h]	16 (5.6)	7 (4.1)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	3 (1.0)	0
Vascular disorders		
Hypertension [i]	5 (1.7)	2 (1.2)

Note: TEAEs are defined as any adverse event that started on or after the first dose of study treatment. Terms are coded using MedDRA v24.1. Percentages are based on the number of subjects in the analysis set. Adverse events are sorted by decreasing frequency of preferred term in the etrasimod treatment group. Subjects are counted only once per summarization level

[a] Bradycardia includes bradycardia and sinus Bradycardia

[b] Urinary tract infection includes urinary tract infection and cystitis

[c] Upper respiratory tract infection includes pharyngitis, rhinorroea and sinusitis

[d] Herpes viral infection includes herpes zoster, oral herpes and herpes simplex

[e] Elevated liver enzymes includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, blood alkaline phosphatase increased, cholestasis, hyperbilirubinaemia and liver function test increased

[f] Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased

[g] Dizziness includes dizziness, dizziness exertional and dizziness postural

[h] Headache includes headache, migraine and tension headache
[i] Hypertension includes hypertension and blood pressure increased

8.3 Less Common Clinical Trial Adverse Reactions

The following is a list of treatment-emergent adverse events reported by patients treated with VELSIPITY 2mg during the Induction and Maintenance studies at an incidence of < 1% but at an incidence of ≥ 0.5% higher in the VELSIPITY group than placebo.
Cardiac disorders: atrioventricular block
Gastrointestinal disorders: abdominal pain lower
Infections and Infestations: anal abscess, hordeolum,
Investigations: blood triglycerides increased,
Metabolism and nutrition disorders: hypophosphataemia
Nervous system disorders: somnolence
Psychiatric disorders: anxiety
Skin and Subcutaneous Tissue Disorders: night sweats

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 4 - Abnormal lab findings with an incidence of greater than or equal to 1% for VELSIPITY and ≥1% higher than placebo- UC 12-week Studies

System Organ Class **Preferred Term**	Etrasimod 2 mg (N = 288) n (%)	Placebo (N = 170) n (%)
Investigations		
Gamma-glutamyl transferase increased	7 (2.4)	0
Blood creatine phosphokinase increased	5 (1.7)	1 (0.6)
Alanine aminotransferase increased	3 (1.0)	0
Metabolism and nutrition disorders		
Hypercholesterolaemia	4 (1.4)	1 (0.6)
Hypophosphataemia	4 (1.4)	0

Table 5 - Abnormal lab findings with an incidence of greater than or equal to 1% for VELSIPITY and ≥1% higher than placebo- UC 52-week Study

System Organ Class **Preferred Term**	Etrasimod 2 mg (N = 289) n (%)	Placebo (N = 144) n (%)
Investigations		
Alanine aminotransferase increased	8 (2.8)	2 (1.4)
Blood creatine phosphokinase increased	5 (1.7)	1 (0.7)
Transaminases increased	3 (1.0)	0
Metabolism and nutrition disorders		
Hypercholesterolaemia	8 (2.8)	0

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Effect of other medicinal products on etrasimod

In vitro studies indicate that metabolism of etrasimod occurs through multiple distinct enzyme systems, including multiple CYP450 (CYP2C8, CYP2C9, and CYP3A4), non-CYP450 oxidative enzymes and UGTs. Metabolism by sulfotransferases was observed in clinical excreta samples based on metabolite profiling. Overall, the disposition of etrasimod is mediated by several enzymes without major contribution by any single enzyme.

Etrasimod is not a substrate of P-gp, BCRP, OATP1B1/3, OAT1/3, or OCT1/2 transporters. Drugs that are inhibitors of these transporters are unlikely to impact the pharmacokinetics of etrasimod.

CYP2C8, CYP2C9 and CYP3A4 inhibitors
The co-administration of etrasimod with steady state fluconazole (moderate CYP2C9 and CYP3A4 inhibitor) increased exposure (AUC) of etrasimod by 84%. Co-administration of VELSIPITY with a therapeutic agent or a combination of agents that are both moderate CYP2C9 and moderate or strong CYP3A4 inhibitors (e.g., fluconazole) increases the exposure of VELSIPITY and is not recommended. The strong CYP2C8 inhibitor gemfibrozil and the strong CYP3A4 inhibitor itraconazole increased exposure (AUC) of etrasimod by 36% and 32%, respectively. These changes in exposure are unlikely to be clinically significant.

CYP2C9 Polymorphisms
In patients who are suspected, or known to be, poor CYP2C9 metabolizers, coadministration of etrasimod with strong CYP2C8 inhibitors or strong CYP3A4 inhibitors is not recommended due to the potential of clinically significant elevated etrasimod exposures.

CYP2C8, CYP2C9, and CYP3A4 inducers
The co-administration of etrasimod with rifampicin (strong CYP3A4, moderate CYP2C8, and CYP2C9 inducer) decreased exposure (AUC) of etrasimod by 49%. Co-administration of VELSIPITY with a therapeutic agent or a combination of agents that are moderate to strong inducers of two or more CYPs (CYP2C8, CYP2C9, and CYP3A4) (e.g., rifampicin) decreases the exposure of VELSIPITY and is not recommended.

Beta blockers and calcium channel blockers
The co-administration of VELSIPITY in patients receiving stable beta blocker treatment did not result in additive effects on heart rate reduction. VELSIPITY can be initiated in patients receiving stable doses of beta blocker treatment. Following the first dose of etrasimod 2 mg, the Day 1 maximum mean change from baseline heart rate reduction in patients on stable beta blocker treatment was comparable to patients not taking a beta blocker (mean [SD]: -6.5 [7.15] bpm compared with -7.2 [9.27] bpm).

The initiation of a beta blocker with stable treatment of VELSIPITY has not been studied.

The effect of co-administration of VELSIPITY and a calcium channel blocker has not been studied.

Anti-arrhythmic drugs, QT prolonging drugs, drugs that may decrease heart rate

VELSIPITY has not been studied in patients taking QT prolonging drugs.
Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with VELSIPITY is considered in patients on Class Ia or Class III anti-arrhythmic drugs, advice from a cardiologist should be sought (see **7 WARNINGS AND PRECAUTIONS**).

Because of the potential additive effects on heart rate and/or QT interval, if treatment initiation with VELSIPITY is considered in patients on QT prolonging drugs, advice from a cardiologist should be sought (see **7 WARNINGS AND PRECAUTIONS**).

Anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies
VELSIPITY is contraindicated in patients with increased risk of opportunistic infections, including those who are immunocompromised due to treatment (e.g., antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g., immunodeficiency syndrome) immunodeficient state. (see **2 CONTRAINDICATIONS** and **7 WARNINGS AND PRECAUTIONS**).

Vaccination
Vaccinations may be less effective if administered during and for up to 2 weeks after discontinuation of treatment with VELSIPITY. The use of live attenuated vaccine may carry the risk of infection and should therefore be avoided during VELSIPITY treatment and for 2 weeks after discontinuation of treatment with VELSIPITY (see **7 WARNINGS AND PRECAUTIONS**).

Effect of etrasimod on other drugs
In vitro studies indicate that at the recommended dose of 2 mg once daily, etrasimod is unlikely to show any clinically relevant drug-drug interaction potential for CYPs or membrane transporters. and therefore not expected to impact exposures of coadministered drugs.

Oral contraceptives
No clinically significant differences in the pharmacokinetics and pharmacodynamics of an oral contraceptive containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel were observed when coadministered with etrasimod. In patients susceptible to oral contraceptive-induced elevated liver enzymes and cholestasis, the risk may be increased by etrasimod coadministration.

Table 6 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Strong CYP2C8 inhibitor (e.g. gemfibrozil)	CT	Coadministration of etrasimod 1 mg with gemfibrozil a strong CYP2C8 inhibitor increased etrasimod exposure by 36%	Coadministration of VELSIPITY with a strong CYP2C8 inhibitor is unlikely to result in any clinically significant drug-drug interactions. In patients who are poor CYP2C9 metabolizers, coadministration of VELSIPITY with a strong CYP2C8 inhibitor is not recommended.

CYP2C9 and CYP3A4 inhibitor (e.g. fluconazole)	CT	Coadministration of etrasimod 1 mg with fluconazole a moderate CYP2C9 and CYP3A4 inhibitor increased etrasimod exposure by 84%.	Coadministration of VELSIPITY with a therapeutic agent or a combination of agents that are both moderate CYP2C9 and moderate or strong CYP3A4 inhibitor is not recommended.
Strong CYP3A4 inhibitor (e.g. itraconazole)	CT	Coadministration of etrasimod 1 mg with itraconazole a strong CYP3A4 inhibitor increased etrasimod exposure by 32%.	Coadministration of VELSIPITY with a strong CYP3A4 inhibitor is unlikely to result in any clinically significant drug-drug interactions. In patients who are poor CYP2C9 metabolizers, coadministration of VELSIPITY with a strong CYP3A4 inhibitor is not recommended.
Strong CYP3A4, moderate CYP2C8 and CYP2C9 inducer (e.g. rifampicin)	CT	Coadministration of etrasimod 2 mg with rifampicin a strong CYP3A4, moderate CYP2C8 and CYP2C9 inducer decreased etrasimod exposure by 49%.	Coadministration of VELSIPITY with a therapeutic agent or a combination of agents that are both moderate CYP2C8 or CYP2C9 and strong CYP3A4 inducers (e.g. rifampicin) is not recommended.

Legend: CT = Clinical Trial

9.5 Drug-Food Interactions

Food (high-fat meal) intake had no effect on etrasimod exposure (C_{max} and AUC)

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Etrasimod is a sphingosine 1-phosphate receptor modulator that exhibits selectivity to S1P receptors 1, 4 and 5 (S1P1,4,5), with no activation of S1P2 receptors and minimal activation of S1P3 receptors. At the S1P1 receptor, etrasimod activates G-protein signalling and beta-arrestin recruitment. Etrasimod partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood thereby lowering the number of activated lymphocytes in the tissue.

The mechanism by which etrasimod exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into sites of inflammation. The etrasimod-induced reduction of

lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Etrasimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance.

10.2 Pharmacodynamics

Heart rate and rhythm
VELSIPITY may result in a transient decrease in heart rate and AV conduction upon treatment initiation (see **7 WARNINGS AND PRECAUTIONS** and **8 ADVERSE EVENTS**). On Day 1, in UC patients from ELEVATE UC 52 and ELEVATE UC 12, the greatest mean decrease in heart rate was 7.3 bpm and observed at Hour 2 or 3 post dose.

Effect on PR interval
Post 1st dose of etrasimod mean (SD) change in PR interval from pre-dose to 4 hours post dose with etrasimod was 5.5 msec (18.4). PR interval prolongation > 200 msec was recorded on ECG in 5.1% and higher degree prolongation (> 230 msec) in 1.8% of subjects in ELEVATE UC 52 and ELEVATE UC 12.

All PR interval prolongations (including those reported as adverse events) post 1st dose of etrasimod on Study Day 1 were overall transient, asymptomatic, did not require any treatment and participants remained hemodynamically stable.

Effect on QT interval
Exposure-response modelling showed that at plasma concentrations approximately 1.4-fold higher than expected clinically, the placebo-corrected, change from baseline increase in QTcF was 4.3msec (90% CI: 1.46, 7.18). Advice from a cardiologist should be sought prior to initiation of VELSIPITY treatment in patients with significant QT prolongation (QTcF ≥ 450 msec in males, ≥ 470 msec in females), or in patients receiving QT prolonging drugs or Class Ia or Class III anti-arrhythmic drugs because of the potential for these patients to exceed acceptable QTcF intervals (see **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS**).

Reduction in blood lymphocyte counts
In controlled clinical studies, mean lymphocyte counts decreased to approximately 50% of baseline at 2 weeks (approximate mean blood lymphocyte counts 0.9 x 109/L) consistent with the mechanism of action, and lowered lymphocyte counts were maintained during once daily treatment with VELSIPITY.

Peripheral blood B cells [CD19+] and T cells [CD3+], T-helper [CD3+CD4+], and T-cytotoxic [CD3+CD8+] cell subsets were all reduced, while natural killer cells and monocytes were not. T-helper cells were more sensitive to the effects of etrasimod than T-cytotoxic cells.

Peripheral blood absolute lymphocyte counts returned to the normal range in 90% of patients within 1 to 2 weeks of stopping therapy based on a population pharmacokinetic/pharmacodynamic model.

Reduction in tissue lymphocyte counts
In ELEVATE UC 52 and ELEVATE UC 12, etrasimod reduced activated lymphocytes in colon biopsies from patients with UC.

Peripheral inflammatory proteins
Etrasimod reduces peripheral inflammatory proteins including those related to UC.

Fecal Calprotectin (FCP)
In controlled clinical studies, treatment with etrasimod resulted in a reduction from baseline of fecal calprotectin at Week 12 compared to placebo.

Pulmonary function
Reductions in FEV1 and FVC were observed in patients treated with VELSIPITY. In ELEVATE UC 52 and ELEVATE UC 12, by week 12, the absolute change in mean FEV1 in patients treated with etrasimod was -49 mL, compared to -19 mL for placebo. There was no further decline relative to placebo by week 52. By week 12 the absolute change in mean FVC in patients treated with etrasimod was -12 mL, compared to - 5 mL for placebo, and at week 52 it was -39 mL vs 8 mL. The absolute change in mean FEV1/FVC in patients treated with VELSIPITY was 0.026, compared to 0.024 for placebo. There was no further decline relative to placebo by week 52.

10.3 Pharmacokinetics

Following etrasimod single oral dosing, C_{max} and AUC increased approximately dose-proportionally in the dose-range studied (0.1 mg to 5 mg). Following multiple dosing, mean C_{max} and AUC increased slightly more than dose proportional from 0.7 mg to 2 mg.

Steady state plasma concentrations are reached within 7 days following 2 mg once daily dosing, with a mean C_{max} of 113 ng/mL and AUC_{tau} of 2163 h*ng/mL. Steady state etrasimod accumulation is approximately 2- to 3-fold greater than single dose.

The pharmacokinetics of VELSIPITY is similar in healthy subjects and subjects with UC (See Table 7).

Table 7- Summary of etrasimod Mean (SD) Pharmacokinetic Parameters in Healthy Subjects Following Oral Dosing of VELSIPITY 2 mg Once Daily for 21 Days

	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{½}$ (h)	AUC_{0-24} (ng·h/mL)	CLss/F (L/h)	Vz/F (L)
Etrasimod	113 (27.5)	8.0 (2.0-8.00)	46.4 (7.8)	2163 (489)	0.98 (0.27)	66.2 (23.9)

[a]Median (min-max)

Absorption

The time (T_{max}) to reach maximum plasma concentrations (C_{max}) after oral administration of immediate release oral dosage forms of etrasimod is approximately 4 hours (range 2 – 8 hours). Etrasimod absorption is extensive, based on high permeability and observation of relatively little intact etrasimod eliminated in the feces (11.2% of administered radioactive dose). Steady-state exposure was reached within 7 days of dose initiation of etrasimod.

Effect of food

Administration of etrasimod with food slightly delayed absorption (the median T_{max} increased by 2 hours). Food does not have an effect on etrasimod exposure measures (C_{max} and AUC); therefore, etrasimod can be administered without regard to meals.

Distribution:

Etrasimod distributes to body tissues with a mean oral volume of distribution (Vz/F) of 66 L. Etrasimod is highly protein bound, 97.9% to human plasma protein and mainly distributed in the plasma fraction

of whole blood.

Metabolism:

Etrasimod is metabolized by oxidation and dehydrogenation mediated primarily by CYP2C8 (38%), CYP2C9 (37%), and CYP3A4 (22%), with minor contributions of CYP2C19 and CYP2J2. In addition, etrasimod undergoes glucuronidation and sulfation mediated by UGTs and sulfotransferases. Unchanged etrasimod is the major circulating component in plasma.

Elimination

After oral administration, the apparent steady state oral clearance (CL/F) was approximately 1 L/h. The mean plasma effective elimination half-life ($t_{1/2}$) of etrasimod is approximately 30 hours. The primary route of excretion of etrasimod is via the hepatobiliary pathway. Administration of a radioactive single dose resulted in 82% being recovered in the feces and 4.9% being recovered in the urine after 336 hours. 11.2% of the recovered dose in feces was unchanged etrasimod, while no unchanged etrasimod was detected in urine.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of VELSIPITY in children and adolescents have not been established.
- **Geriatrics:** Population pharmacokinetic analyses showed that age did not have an effect on the pharmacokinetics of etrasimod in patients over 65 years of age. There is no meaningful difference in the pharmacokinetics in elderly patients compared to younger patients.
- **Sex:** Sex has no clinically significant influence on etrasimod pharmacokinetics.
- **Ethnic Origin:** No clinically relevant pharmacokinetic differences were observed between Japanese, Chinese, and Caucasian patients.
- **Hepatic Insufficiency:** Use of VELSIPITY in patients with severe hepatic impairment is not recommended. No dosage adjustment is needed in patients with mild to moderate hepatic impairment. The total etrasimod exposure (AUC) are 13%, 29%, and 57% higher in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with subjects with normal liver function for the 2 mg single dose studied. The unbound etrasimod AUC in subjects with mild, moderate, and severe hepatic impairment was similar to subjects with normal liver function.
- **Renal Insufficiency:** No dose adjustments are needed in patients with renal impairment as Cmax and AUC were comparable between subjects with severe renal impairment (comprised of subjects with eGFR ≤ 29 mL/min) and subjects with normal renal function. The effect of hemodialysis on the pharmacokinetics of etrasimod was not evaluated.
- **Body weight:** Based on a population pharmacokinetic analysis, the predicted steady-state Cmax and AUC values of etrasimod are 25% and 23% higher in a low weight individual (50 kg) and 25.9% and 24.3% lower in a high weight individual (110 kg) compared to those in a reference individual (70 kg), respectively. The differences in Etrasimod exposure by body weight are not clinically significant.

11 STORAGE, STABILITY AND DISPOSAL

VELSIPITY does not require any special storage conditions.

Store VELSIPITY at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

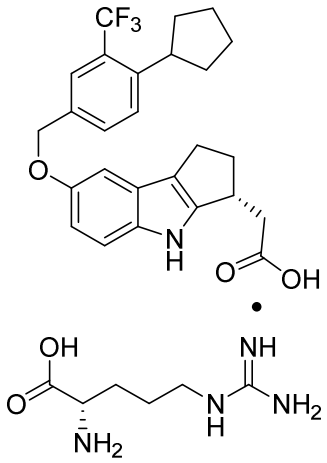
Drug Substance

Proper/Common name: etrasimod L-arginine

Chemical name: L-arginine salt of (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl) acetic acid

Molecular formula and molecular mass: $C_{32}H_{40}F_3N_5O_5$ and 631.69 g/mol

Structural formula:



Physicochemical properties: Etrasimod L-arginine is a white, off-white to light brown solid that is slightly soluble in water.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Description of Clinical Studies

The efficacy of VELSIPITY was evaluated in 2 randomized, double-blind, placebo-controlled clinical studies (ELEVATE UC 52 and ELEVATE UC 12) in patients 16 to 80 years of age with moderately to severely active ulcerative colitis (See Table 8).

Both studies included patients who had an inadequate response, loss of response, or intolerance to one or more of the following treatment options: oral aminosalicylates, corticosteroids, thiopurines, Janus kinase (JAK) inhibitors, or a biologic (e.g., TNF blocker, anti-integrin, anti-IL12/23). Enrolled patients had UC confirmed by endoscopy and histopathology with the extent of disease being ≥ 10 cm from the anal verge. Patients with isolated proctitis were also included in the study provided they met all other inclusion criteria.

Disease severity was assessed on the modified Mayo score (mMS), a 3-component Mayo score (0 to 9) which consists of the following subscores (0 to 3 for each subscore): 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. Enrolled patients had a mMS of 4 to 9 with an ES ≥ 2 and RB subscore ≥ 1.

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

Table 8 - Summary of patient demographics for clinical trials in ulcerative colitis

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
APD334-301 (ELEVATE UC 52)	Phase 3, randomized, double-blind, Placebo -controlled, 52-week study	Etrasimod IR tablet Etrasimod 2 mg or Placebo once daily for 52 weeks	433 subjects	40.4 (17 to 78) years of age	Etrasimod: 289 subjects (152 M/137 F) PBO: 144 subjects (88 M/56 F)
APD334-302 (ELEVATE UC 12)	Phase 3, randomized, double-blind, Placebo -controlled, 12-week study	Etrasimod IR tablet Etrasimod 2 mg or Placebo once daily for 12 weeks	354 subjects	40.4 (16 to 73) years of age	Etrasimod: 238 subjects (135 M/103 F) PBO: 116 subjects (73 M/43 F)

ELEVATE UC 52

ELEVATE UC 52 was a treat-through study, with a total of 433 patients randomized to receive VELSIPITY 2 mg or placebo at a 2:1 ratio administered orally once daily. Patients remained on their assigned treatment for the duration of the study.

At baseline, enrolled patients had a median mMS of 7, with 5.5% of patients having mMS of 4, 66.5% having mMS 5 to 7 (moderately active disease), and 28% having mMS > 7 (severely active disease). 8% of enrolled patients presented with isolated proctitis. A total of 30% of patients had prior exposure to biologic/JAK inhibitors; a total of 14% of patients had exposure to > 1 biologic/JAK inhibitor and 11% of patients had prior exposure to anti-integrins. At baseline, 77% of patients were receiving oral aminosalicylates and 31% of patients were receiving oral corticosteroids.

The co-primary endpoints were the proportion of patients achieving clinical remission at Week 12 and at Week 52, with clinical remission defined as SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline), RB subscore of 0, and ES ≤ 1 (excluding friability). The secondary endpoints included the proportion of patients achieving endoscopic improvement, symptomatic remission, histologic-endoscopic mucosal improvement, clinical response, corticosteroid-free clinical remission, and sustained clinical remission. The primary analysis was conducted at Week 12 and at Week 52 in patients with moderately to severely active disease, defined as mMS 5 to 9 (see Table 9).
A significantly greater proportion of patients treated with etrasimod achieved clinical remission,

endoscopic improvement, symptomatic remission, and histologic-endoscopic mucosal improvement at Week 12 and at Week 52, corticosteroid-free clinical remission and sustained clinical remission at Week 52, compared to placebo (see Table 9).

Table 9: Proportion of patients meeting efficacy endpoints at Week 12 and at Week 52 in ELEVATE UC 52

	Placebo N = 135		VELSIPITY N = 274		Treatment Difference (95% CI)[a]
	n	%	n	%	
Week 12 Endpoints					
Clinical Remission[b] (Primary endpoint)	**10**	**7%**	**74**	**27%**	**20% (13%, 27%) p<0.001**
No prior biologic/ JAK inhibitor exposure	9/93	10%	60/194	31%	21% (13%, 30%) p<0.001
Prior biologic/ JAK inhibitor exposure	1/42	2%	14/80	18%	15% (5%, 25%) p=0.004
Endoscopic Improvement[c]	**19**	**14%**	**96**	**35%**	**21% (13%, 29%) p<0.001**
No prior biologic/ JAK inhibitor exposure	17/93	18%	76/194	39%	21% (11%, 31%) p<0.001
Prior biologic/ JAK inhibitor exposure	2/42	5%	20/80	25%	19% (7%, 31%) p=0.002
Symptomatic Remission[d]	**29**	**22%**	**126**	**46%**	**25% (15%, 34%) p<0.001**
No prior biologic/ JAK inhibitor exposure	22/93	24%	101/194	52%	29% (18%, 40%) p<0.001
Prior biologic/ JAK inhibitor exposure	7/42	17%	25/80	31%	13% (-2%, 28%) p=0.078
Histologic-endoscopic mucosal improvement[e]	**6**	**4%**	**58**	**21%**	**17% (11%, 23%) p<0.001**
No prior biologic/ JAK inhibitor exposure	6/93	7%	47/194	24%	18% (10%, 26%) p<0.001
Prior biologic/ JAK inhibitor exposure	0/42	0%	11/80	14%	14% (6%, 22%) p<0.001
Week 52 Endpoints					

Clinical Remission[b] (Primary endpoint)	**9**	**7%**	**88**	**32%**	**25% (18%, 32%) p<0.001**
No prior biologic/ JAK inhibitor exposure	7/93	8%	71/194	37%	29% (20%, 38%) p<0.001
Prior biologic/ JAK inhibitor exposure	2/42	5%	17/80	21%	15% (3%, 26%) p=0.011
Endoscopic Improvement[c]	**14**	**10%**	**102**	**37%**	**27% (19%, 34%) p<0.001**
No prior biologic/ JAK inhibitor exposure	12/93	13%	78/194	40%	28% (19%, 38%) p<0.001
Prior biologic/ JAK inhibitor exposure	2/42	5%	24/80	30%	23% (11%, 35%) p<0.001
Symptomatic Remission[d]	**25**	**19%**	**119**	**43%**	**25% (16%, 34%) p<0.001**
No prior biologic/ JAK inhibitor exposure	19/93	20%	97/194	50%	29% (18%, 40%) p<0.001
Prior biologic/ JAK inhibitor exposure	6/42	14%	22/80	28%	11% (-3%, 26%) p=0.126
Histologic-endoscopic mucosal improvement[e]	**11**	**8%**	**73**	**27%**	**18% (11%, 25%) p<0.001**
No prior biologic/ JAK inhibitor exposure	10/93	11%	55/194	28%	19% (10%, 27%) p<0.001
Prior biologic/ JAK inhibitor exposure	1/42	2%	18/80	23%	19% (9%, 30%) p<0.001
Corticosteroid-free Clinical Remission[f]	**9**	**7%**	**88**	**32%**	**25% (18%, 32%) p<0.001**
No prior biologic/ JAK inhibitor exposure	7/93	8%	71/194	37%	29% (20%, 38%) p<0.001
Prior biologic/ JAK inhibitor exposure	2/42	5%	17/80	21%	15% (3%, 26%) p=0.011
Maintenance of Clinical Remission[g]	**3**	**2%**	**49**	**18%**	**16% (11%, 21%) p<0.001**
No prior biologic/ JAK inhibitor exposure	2/93	2%	41/194	21%	19% p<0.001

Prior biologic/ JAK inhibitor exposure	1/42	2%	8/80	10%	7% (-1%, 16%) p=0.092

CI = confidence interval

[a] Treatment difference (adjusted for stratification factors of prior biologic/JAK inhibitor exposure, corticosteroid use at baseline, and baseline mMS group).

[b] Clinical remission was defined as SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline), RB subscore of 0, and ES ≤ 1 (excluding friability).

[c] Endoscopic improvement was defined as ES ≤ 1 (excluding friability).

[d] Symptomatic remission was defined as SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline) and RB subscore of 0.

[e] Histologic-endoscopic mucosal improvement was defined as ES ≤ 1 (excluding friability) with histologic remission (Geboes Index score < 2.0, indicating no neutrophils in the epithelial crypts or lamina propria, no increase in eosinophils, and no crypt destruction, erosions, ulcerations, or granulation tissue).

f Corticosteroid-free clinical remission was defined as clinical remission at Week 52 without receiving corticosteroids for at least 12 weeks prior to Week 52.

g Maintenance of clinical remission was defined as clinical remission at both Week 12 and Week 52.

Isolated proctitis

A greater proportion of patients with isolated proctitis at baseline treated with VELSIPITY compared to placebo achieved clinical remission at Week 12 (11 (46%) vs 2 (29%)) and Week 52 (10 (42%) vs 1 (14%)).

Corticosteroid-free clinical remission among patients treated with corticosteroids at baseline

At Week 52, a greater proportion of patients treated with VELSIPITY achieved corticosteroid-free clinical remission (defined as clinical remission at Week 52 without receiving corticosteroids for at least 12 weeks prior to Week 52) among patients treated with corticosteroids at baseline compared to placebo (n = 27 of 87, 31% vs n = 3 of 40, 8%).

Symptomatic remission by Week 2

At Week 2 (first study visit), a greater proportion of patients treated with VELSIPITY compared to placebo achieved symptomatic remission (16% vs 11%).

ELEVATE UC 12

In ELEVATE UC 12, a total of 354 patients were randomized to receive VELSIPITY 2 mg or placebo at a 2:1 ratio administered orally once daily.

At baseline, enrolled patients had a median mMS of 7, with 5.6% of patients having mMS of 4, and 67% having mMS 5 to 7 (moderately active disease), and 27.4% having mMS > 7 (severely active disease). 8% of enrolled patients presented with isolated proctitis. A total of 33% of patients had prior exposure to biologic/JAK inhibitors; a total of 18% of patients had exposure to > 1 biologic/JAK inhibitor and 12% of patients had prior exposure to anti-integrins. At baseline, 83% of patients were receiving oral aminosalicylates and 28% of patients were receiving oral corticosteroids.

The primary endpoint was the proportion of patients achieving clinical remission at Week 12. The secondary endpoints included the proportion of patients achieving endoscopic improvement, symptomatic remission, and mucosal healing at Week 12. The primary analysis was conducted at Week 12 in patients with moderately to severely active disease, defined as mMS 5 to 9 (see Table 10).

A significantly greater proportion of patients treated with VELSIPITY achieved clinical remission, endoscopic improvement, symptomatic remission, and histologic-endoscopic mucosal improvement compared to placebo at Week 12 (see Table 10).

Table 10 - Proportion of patients meeting efficacy endpoints at Week 12 in ELEVATE UC 12

Endpoints	Placebo N = 112		VELSIPITY N = 222		Treatment Difference (95% CI)[a]
	N	%	n	%	
Clinical Remission[b] (Primary endpoint)	**17**	**15%**	**55**	**25%**	**10% (1%, 18%) p = 0.026**
No prior biologic/JAK inhibitor exposure	12/74	16%	41/148	28%	12% (1%, 23%) p=0.033
Prior biologic/JAK inhibitor exposure	5/38	13%	14/74	19%	7% (-7%, 20%) p=0.349
Endoscopic Improvement[c]	**21**	**19%**	**68**	**31%**	**12% (3%, 21%) p = 0.009**
No prior biologic/JAK inhibitor exposure	14/74	19%	51/148	35%	16% (5%, 27%) p=0.005
Prior biologic/JAK inhibitor exposure	7/38	18%	17/74	23%	5% (-10%, 21%) P=0.487
Symptomatic Remission[d]	**33**	**30%**	**104**	**47%**	**17% (7%, 28%) p = 0.001**
No prior biologic/JAK inhibitor exposure	23/74	31%	73/148	49%	18% (5%, 32%) p=0.006
Prior biologic/JAK inhibitor exposure	10/38	26%	31/74	42%	17% (0%, 35%) P=0.054
Histologic-endoscopic mucosal improvement[e]	**10**	**9%**	**36**	**16%**	**7% (1%, 14%) p = 0.036**
No prior biologic/JAK inhibitor exposure	8/74	11%	28/148	19%	8% (-1%, 18%) p=0.071
Prior biologic/JAK inhibitor exposure	2/38	5%	8/74	11%	6% (-4%, 16%) P=0.233

CI = confidence interval

[a] Treatment difference (adjusted for stratification factors of prior biologic/JAK inhibitor exposure, corticosteroid use at baseline, and baseline mMS group).

[b] Clinical remission was defined as SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline), RB subscore of 0, and ES ≤ 1 (excluding friability).

[c] Endoscopic improvement was defined as ES ≤ 1 (excluding friability).

[d] Symptomatic remission was defined as SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline) and RB subscore of 0.

[e] Histologic-endoscopic mucosal improvement was defined as ES ≤ 1 (excluding friability) with histologic remission (Geboes Index score < 2.0, indicating no neutrophils in the epithelial crypts or lamina propria, no increase in eosinophils, and no crypt destruction, erosions, ulcerations, or granulation tissue).

Isolated proctitis
A greater proportion of patients with isolated proctitis at baseline treated with VELSIPITY compared to placebo achieved clinical remission at Week 12 (5 (39%) vs 1 (8%)).

Symptomatic remission by Week 4
At Week 4, a greater proportion of patients treated with VELSIPITY compared to placebo achieved symptomatic remission (28% vs 16%).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Repeat-dose toxicity studies for up to 6 months in rats, 9 months in dogs and 91 days in mice were found with the no observed adverse effect levels (NOAELs) to be ≥102 times the exposure at RHD. Non-adverse effects were commonly associated with other S1P modulators, including reductions in lymphoid cell populations in lymphoid tissues, erythrocytosis or erythrophagocytosis were observed in treatment groups across all species. Higher lung weights with or without microscopic findings (alveolar histiocytosis, fibrin deposition, fibrosis of pleura), centrilobular/panlobular hepatocyte hypertrophy, and lower body weights were also observed. Treatment-related effects in the left ventricular arteries (hypertrophy/hyperplasia of the tunica media) were also observed in 3- and 9-month repeat-dose toxicity studies in dogs at ≥24 times RHD exposure in humans based on AUC.

Genotoxicity:
Etrasimod was negative in a battery of *in vitro* (Ames, chromosomal aberration in human peripheral blood lymphocytes) and *in vivo* (rat micronucleus) assays.

Carcinogenicity:
Oral carcinogenicity studies of etrasimod were conducted in mice and rats. In mice administered etrasimod (0, 2, 6, or 20 mg/kg/day) for up to 104 weeks, there was an increase in hemangiosarcoma and hemangioma at 6 and 20 mg/kg/day in males and females. The no-observed-effect level for tumours was 2 mg/kg/day (19 times that in humans at the recommended human dose (RHD). In rats, oral administration of etrasimod (0, 2, 6, or 20 mg/kg/day) for up to 91 weeks, did not result in an increase in tumors. Plasma VELSIPITY exposure (AUC) at the highest dose tested in male and female rats is approximately 80 to 179 times (respectively) that in humans at the RHD.

Reproductive and Developmental Toxicology:
When etrasimod was administered orally to male (0, 25, 100, or 200 mg/kg/day) and female (0, 1, 2, or 4 mg/kg/day) rats daily from pre-mating to conception and conception to implantation, there were no adverse effects observed on male or female fertility. Plasma etrasimod exposure (AUC) at the highest dose tested was approximately 467 (males) and 21 (females) times that in humans at the RHD.

When etrasimod (0, 1, 2, or 4 mg/kg/day) was orally administered to pregnant rats during the period of organogenesis, post-implantation loss with a corresponding lower mean number of viable fetuses was observed at 4 mg/kg/day. Etrasimod-related fetal external (4 mg/kg/day) and visceral (all dose levels) malformations and skeletal variations (2 and 4 mg/kg/day) were noted. At ≥1 mg/kg/day (the lowest

dose tested), the visceral malformations of aorticopulmonary septal defect, as well as the developmental variation of short brachiocephalic trunk were observed. A NOAEL was not established in this study, and maternal plasma AUC at 1 mg/kg/day was approximately 5 times that in humans at the RHD of 2 mg/day.

When etrasimod (0, 2, 10, or 20 mg/kg/day) was orally administered to pregnant rabbits during the period of organogenesis, postimplantation loss with a corresponding lower mean number of viable fetuses was observed at 10 and 20 mg/kg/day. Etrasimod-related fetal visceral malformations of the aortic arch (bulbous aortic arch and/or coarctation of the aortic arch) were observed at ≥10 mg/kg/day and fetal skeletal malformations (fused sternebrae) at 20 mg/kg/day. There were no effects on embryofetal development at 2 mg/kg/day. Maternal plasma exposure (AUC) at the NOAEL dose (2 mg/kg/day) was approximately 0.8 times that in humans at the RHD of 2 mg/day.

Oral administration of etrasimod (0, 0.4, 2, or 4 mg/kg/day) to female rats throughout pregnancy and lactation resulted in increased gestation length in F0 dams at 2 and 4 mg/kg/day, decreased mean pup weights at all dose levels during the preweaning period, lower pup viability at 2 and 4 mg/kg/day, lower pup survival during the lactation period at 4 mg/kg/day, and reduced fertility and reproductive performance (reduction in implantations and increased preimplantation loss) in F1 pups at the highest dose tested. No effects were noted on neurobehavioral function in offspring at any dose level tested. Plasma exposure (AUC) in dams at the NOAEL was equivalent (1.1 times) to those in humans at the RHD. Etrasimod was detected in the plasma of F1 pups, indicating exposure from the milk of the lactating dam.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

VELSIPITY

etrasimod (as etrasimod L-arginine)

Read this carefully before you start taking etrasimod and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about etrasimod.

What is VELSIPITY used for?

VELSIPITY is used to treat adult patients with moderately to severely active ulcerative colitis (UC). It is used when a patient's UC is still active after other treatments have not worked or were not tolerated.

How does VELSIPITY work?

VELSIPITY helps reduce inflammation in the gut. It works by stopping certain white blood cells from reaching the lining of the gut.

What are the ingredients in VELSIPITY?

Medicinal ingredients: etrasimod (as etrasimod L-arginine)
Non-medicinal ingredients:
Tablet core contains magnesium stearate, mannitol, microcrystalline cellulose, sodium starch glycolate.
Tablet coating contains FD&C blue #1/brilliant blue FCF aluminum lake, FD&C blue #2/indigo carmine aluminum lake, FD&C yellow #5/tartrazine aluminum lake, macrogol 4000 JP/PEG 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

VELSIPITY comes in the following dosage forms:

Tablet, 2 mg etrasimod (as etrasimod L-arginine)

Do not use VELSIPITY if:

- you are allergic to etrasimod or to any of the other ingredients in VELSIPITY.
- you have an increased risk of infection because:
    - you have a condition that weakens your immune system or because
    - you take a medicine or receive a treatment that weakens your immune system.
- you have had a heart attack, chest pain, a stroke or mini-stroke, or certain types of severe heart failure in the last 6 months.
- you have certain types of irregular or abnormal heartbeats called an arrhythmia.
- you have a severe active infection or an active chronic infection.
- you have cancer.
- you are pregnant or a woman of childbearing potential not using effective birth control.
- you are breastfeeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VELSIPITY. Talk about any health conditions or problems you may have, including if you:

- have a slow heart rate or you are taking or have recently taken medicines that slow your heart rate.

- have had symptoms of a slow heart rate such as dizziness, tiredness, confusion or fainting.
- have recently taken medicines to support a better impulse of your heartbeat such as beta blockers or calcium channel blockers.
- have an irregular heart rhythm (unless you have a working pacemaker).
- have episodes of sudden loss of consciousness known as fainting.
- have untreated sleep apnea.
- have ever had a stroke or other diseases related to blood vessels in the brain.
- have reduced blood flow to your heart or have ever had a heart failure.
- Have ever had a heart attack.
- have liver problems.
- have an infection.
- have low levels of white blood cells called lymphocytes.
- have recently had or are planning to have a vaccination since VELSIPITY may make vaccines less effective.
- have or have had problems with your vision.
- have inflammation of the eye.
- have diabetes.
- have high blood pressure.
- have severe lung disease such as pulmonary fibrosis, asthma, or chronic obstructive pulmonary disease.
- have a fever or high temperature.

Other warnings you should know about:

Slow heart rate and heart problems: Before you start taking VELSIPITY, your healthcare professional will check your heart using a test called an electrocardiogram (ECG) to check if you have any heart problems. This is because when you start taking VELSIPITY, your heart rate might decrease, or the impulse of your heartbeat might decrease. Talk to your healthcare professional if you get any symptoms of bradycardia (slow heart rate). These include: dizziness, tiredness, confusion, fainting, feeling lightheaded, feeling like your heart is beating slowly or skipping beats, shortness of breath, chest pain. You might also experience a slow heart rate and not have any symptoms. Your healthcare professional might also check your blood pressure while you are taking VELSIPITY. This is because VELSIPITY can increase your blood pressure.

Infections: Before you start taking VELSIPITY, tell your healthcare professional if you have an infection. You must not take VELSIPITY if have a severe active infection or an active chronic infection. VELSIPITY lowers the number of white blood cells in your blood. This can increase your risk of getting an infection. This includes serious infections that can be life-threatening and cause death. You are more likely to get an infection while you are taking VELSIPITY and for 5 weeks after you stop taking it. Your healthcare professional may test your white blood cell levels before you start taking VELSIPTY. Talk to your healthcare professional right away if you get any symptoms of an infection while you are taking VELSIPTY and for 5 weeks after you stop taking it. These include: fever, chills, headache, feeling very tired, flu-like symptoms, nausea, swollen lymph nodes. Your healthcare professional might stop or pause your treatment with VELSIPTY if you get an infection.

Cancer: Before you take VELSIPITY, tell your healthcare professional if you have cancer. You must not take VESIPITY if you have cancer. Before you start taking VELSIPITY or soon after you start taking it,

your healthcare professional may examine your skin. Your skin may be looked at by your healthcare professional from time to time to look for any skin lesions or moles, especially if you have risk factors for skin cancer. If you find a mole, contact your healthcare professional right away so that they can look at it. Limit how much time you spend in the sun by wearing clothes that protect your skin and by using sunscreen with a high protection factor (also known as SPF).

Progressive multifocal leukoencephalopathy (PML): PML is a serious viral brain infection that may lead to severe disability or death. Cases of PML have been reported with medicines similar to VELSIPITY. Symptoms of PML include vision problems, weakness in the arms or legs that gets worse, clumsiness, lack of coordination, memory loss or confusion, problems speaking and personality changes. If you get any of these symptoms, talk to your healthcare professional straight away. If your healthcare professional think you might have PML, they will examine you further and may stop your treatment with VELSIPITY.

Posterior reversible encephalopathy syndrome (PRES): Rare cases of PRES have been observed in similar medicines as VELSIPITY. During treatment with VELSIPITY, if you develop any possible symptoms of PRES, speak to your healthcare professional straight away. Symptoms include:sudden severe headache, feeling nauseous or throwing up, confusion, drowsiness, personality change, paralysis, abnormal speech, convulsions and vision changes. In case you experience any of these symptoms, your healthcare professional should urgently examine how your brain is functioning, as these symptoms may be due to a condition called posterior reversible encephalopathy syndrome (PRES). If untreated, PRES may result in a stroke or bleeding in the brain. If your healthcare professional thinks you might have PRES, they will stop your treatment with VELSIPITY.

Testing and monitoring: Before and while taking VELSIPITY, your healthcare professional may check your ability to breathe. They will also perform various blood tests and will interpret the results.

Pregnancy and birth control: You must not take VELSIPITY if you are pregnant or are planning to become pregnant. This is because VELSIPITY can harm an unborn baby. Your healthcare professional will explain the pregnancy risks to you before you start taking VELSIPITY. They will ask you to do a pregnancy test to make sure that you are not pregnant. Your healthcare professional will give you a card which explains why you should not become pregnant while taking VELSIPITY. It also explains what you should do to avoid getting pregnant while you are taking VELSIPITY. You must use effective birth control while you are taking VELSIPITY and for 6 days after you stop taking it. Talk to your healthcare professional about effective birth control methods.

Pregnancy registry: There is a pregnancy exposure registry for women who take VELSIPTY while they are pregnant. The purpose of this registry is to collect information about the health of you and your baby. If you do become pregnant while taking VELSIPITY, talk to your healthcare professional. Talk to them about participating in this registry. You may also call 1-800-616-3791 for more information.
Breastfeeding: Do not take VELSIPITY if you are breastfeeding. This is because VELSIPITY may pass into breast milk.

Driving and using machines: VELSIPITY may cause dizziness, which can affect your ability to drive and use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines

The following may interact with VELSIPITY:

- Medicines used to control your heart rate and blood pressure such as beta blocker medicines and calcium channel blocker medicines.
- Medicines used to control your heart rhythm or heartbeat such as quinidine, procainamide, amiodarone and sotalol.
- Medicines that affect your immune system, including cancer treatment.
- Vaccines.
- Fluconazole, used to treat fungal infections, and other medicines that affect a certain enzyme in your body, can increase the levels of VELSIPITY in the blood. These are not recommended to be taken in combination with VELSIPITY.
- Rifampicin, used to treat bacterial infections, and other medicines that affect a certain enzyme in your body, can decrease the levels of VELSIPITY in the blood. These are not recommended to be taken in combination with VELSIPITY.
- Gemfibrozil, used to treat high cholesterol, and certain other medicines that affect a certain enzyme in the body, can increase the levels of VELSIPITY in the blood for some patients. In these patients, these medicines are not recommended to be taken in combination with VELSIPITY.
- Itraconazole, used to treat fungal infections, and certain other medicines that affect a certain enzyme in the body, can increase the levels of VELSIPITY in the blood for some patients. In these patients, these medicines are not recommended to be taken in combination with VELSIPITY.

How to take VELSIPITY:

- Always take VELSIPITY exactly as your healthcare professional tells you to.
- Swallow tablets whole with water. Do not split, crush, or chew the tablets.
- You can take VELSIPITY with or without food.
- Check with your healthcare professional if you are not sure how to take VELSIPITY.

Usual adult dose:
Take one tablet once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much VELSIPITY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of VELSIPITY, take it as soon as you remember on that day. If you forget to take VELSIPITY for the whole day, skip the missed dose. Take the next scheduled dose the following day. Do not take a double dose to make up for a forgotten dose.

Contact your healthcare professional to discuss how to restart taking VELSIPITY if:

- You miss a dose for more than 2 days in a row within your first week of taking it or;
- If you miss a dose for more than 7 days in a row at any point.

What are possible side effects from using VELSIPITY?
These are not all the possible side effects you may have when taking VELSIPITY. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- high level of cholesterol in the blood
- headache
- nausea

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Infection: fever, chills, headache, feeling very tired, flu-like symptoms, nausea, swollen lymph nodes.		X	
Lymphopenia (decreased white blood cells):fever, cough, mouth ulcers, get infections more easily.		X	
COMMON			
Urinary tract infection: pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine.		X	
Bradycardia (slow heartbeat): dizziness, tiredness, confusion, fainting, feeling lightheaded, feeling like your heart is beating slowly or skipping beats, shortness of breath, chest pain.		X	
Hypertension (high blood pressure): blurry vision, feeling lightheaded, feeling short of breath, measured high blood pressure, sometimes with headache or nosebleed.		X	
Headache		X	
Feeling dizzy		X	
RARE			
Macular edema (a vision problem): blurriness or shadows in the center of your vision, feeling sensitive to		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
light, a blind spot in the center of your vision, colors look unusual.			
Irregular heartbeat: feeling dizzy or fainting, chest pain, feeling short of breath, feeling like your heart is beating faster, feeling like you might throw up.		X	
Breathing problems: shortness of breath		X	
Liver problems: yellowing of your skin or the whites of your eyes, abnormally dark urine, unexplained nausea or vomiting, tiredness, upper abdominal pain, loss of appetite.		X	
FREQUENCY UNKNOWN			
Posterior Reversible Encephalopathy Syndrome (PRES, swelling and narrowing of blood vessels in your brain): sudden severe headache, feeling nauseous or throwing up, confusion, drowsiness, personality change, paralysis, abnormal speech, convulsions, vision changes.			X
Progressive multifocal leukoencephalopathy (PML, a serious brain infection): vision problems, weakness in the arms or legs that gets worse, clumsiness, lack of coordination, memory loss or confusion, problems speaking, personality changes.			X
Skin cancer: skin lesions or moles that appear or if existing skin lesions change appearances.		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store VELSIPITY at room temperature (15°C to 30°C). Keep out of reach and sight of children.

If you want more information about VELSIPITY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.pfizer.ca, or by calling 1-800-463-6001.

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