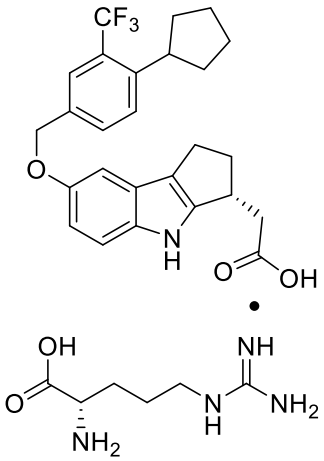
1. NAME OF THE MEDICINAL PRODUCT

VELSIPITY® 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.762 mg of etrasimod L-arginine, equivalent to 2 mg etrasimod.

The chemical structure of etrasimod L-arginine:



3. PHARMACEUTICAL FORM

VELSIPITY is a green, round, film-coated tablet of approximately 6 mm diameter, debossed with “ETR” on one side and “2” on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VELSIPITY is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adult patients who have had an inadequate response to, loss of response to, or intolerance to at least 1 therapy for ulcerative colitis.

4.2. Posology and method of administration

Posology

The recommended dose of VELSIPITY is 2 mg taken orally once daily. VELSIPITY should be swallowed whole and can be administered with or without food (see Section 5.2).

Missed dose
If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled.

Dose interruption
If treatment is interrupted for 7 or more consecutive days, it is recommended to resume treatment with food for the first 3 doses.

Special populations

Elderly
No dose adjustment is needed in patients over 65 years of age.

Etrasimod should be used with caution in elderly patients over 65 years of age, given the limited data available and potential for an increased risk of adverse reactions in this population.

Renal impairment
No dose adjustment is needed for patients with renal impairment (see Section 5.2).

Hepatic impairment
No dose adjustment is needed for patients with mild or moderate hepatic impairment. VELSIPITY should not be used in patients with severe hepatic impairment (see Section 5.2).

Paediatric population
The safety and efficacy of VELSIPITY in children and adolescents have not been established.

4.3. Contraindications

VELSIPITY is contraindicated in the following circumstances:

- Patients who in the last 6 months, have experienced a myocardial infarction, unstable angina pectoris, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation, or New York Heart Association (NYHA) Class III/IV heart failure.
- Patients with a history 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.
- Severe active infections, active chronic infections.
- Severe hepatic impairment.
- During pregnancy and in women of childbearing potential not using effective contraception.
- Active malignancies.

4.4. Special warnings and precautions for use

Bradyarrhythmia and atrioventricular conduction delays

Prior to treatment initiation with etrasimod, an electrocardiogram (ECG) in all patients should be obtained to assess for pre-existing cardiac conduction abnormalities. In patients with certain pre-existing conditions, first dose monitoring is recommended (see below). When re-initiating treatment after an interruption of 7 or more consecutive days, consideration may be given to repeating the baseline ECG and/or monitoring depending on the results of the first evaluation, change in patient characteristics, and duration of interruption.

Initiation of VELSIPITY may result in a transient decrease in heart rate and AV conduction delays (see Section 4.8 and Section 5.1).

On Day 1, after the first dose of VELSIPITY 2 mg in UC patients, the greatest mean decrease from baseline in heart rate was 7.3 beats per minute (bpm) at Hour 3 in ELEVATE UC 52 and Hour 2 in ELEVATE UC 12.

Patients who experienced bradycardia were generally asymptomatic. Few patients experienced symptoms, such as dizziness, and these symptoms resolved without intervention.

First dose monitoring in patients with certain pre-existing cardiac conditions
Due to the risk of transient decreases in heart rate with the initiation of etrasimod, 4-hour monitoring for signs and symptoms of symptomatic bradycardia after the first dose is recommended in patients with resting heart rate <50 bpm, second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure (see Section 4.3).

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 after 4 hours is recommended in patients, if at the end of 4-hour period:

- 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.

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)
- With arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs
- With ischaemic heart disease, heart failure, history of cardiac arrest, cerebrovascular disease, or uncontrolled hypertension
- With history of symptomatic bradycardia, recurrent cardiogenic syncope, or severe untreated sleep apnoea

<u>Infections</u>

Risk of infections
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 (see Section 5.1). VELSIPITY may, therefore, increase the susceptibility to infections (see Section 4.8).

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).

Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts $<0.2 \times 10^9$/L, if confirmed, should lead to interruption of etrasimod therapy until the level reaches $>0.5 \times 10^9$/L when re-initiation of etrasimod can be considered.

The initiation of VELSIPITY in patients with any active infection should be delayed until the infection is resolved.

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 2 weeks after discontinuation of VELSIPITY, vigilance for infection should be continued throughout this period (see Section 5.1).

Progressive multifocal leukoencephalopathy
Progressive multifocal leukoencephalopathy (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 VELSIPITY-treated patients in the development programme; 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 VELSIPITY should be suspended until PML has been excluded by an appropriate diagnostic evaluation. If PML is confirmed, treatment with VELSIPITY should be discontinued.

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 VELSIPITY 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 VELSIPITY (see Section 5.1).

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy.

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

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

Update immunisations in agreement with current immunisation guidelines prior to initiating VELSIPITY therapy.

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 initiating VELSIPITY. A full course of VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with VELSIPITY, following which initiation of treatment with VELSIPITY should be postponed for 4 weeks to allow the full effect of vaccination to occur.

Liver injury

Elevations of aminotransferases may occur in patients receiving VELSIPITY (see Section 4.8).

Recent (i.e., within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with VELSIPITY. In the absence of clinical symptoms, liver transaminases and bilirubin levels should be monitored at Months 1, 3, 6, 9, and 12 on therapy and periodically thereafter.

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 VELSIPITY should be discontinued if significant liver injury is confirmed.

Increased blood pressure

In clinical studies, hypertension was more frequently reported in patients treated with VELSIPITY than in patients treated with placebo (see Section 4.8). Blood pressure should be monitored during treatment with VELSIPITY and managed appropriately.

Foetal risk

Based on animal studies, VELSIPITY may cause foetal harm (see Section 4.6 and Section 5.3). Before initiation of VELSIPITY treatment, women of childbearing potential must be counselled on the potential for a serious risk to the foetus and the need for effective contraception during treatment with VELSIPITY, and must have a negative pregnancy test.

Because it takes time to eliminate VELSIPITY from the body, women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 10 days after stopping VELSIPITY (see Section 4.6).

If a woman becomes pregnant while on treatment, VELSIPITY must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and ultrasonography examinations should be performed.

Macular oedema

S1P receptor modulators, including VELSIPITY, have been associated with an increased risk of macular oedema (see Section 4.8).

An ophthalmic evaluation of the fundus, including the macula, is recommended near the start of treatment in all patients and at any time if there is any change in vision while taking VELSIPITY.

Patients with a history of diabetes mellitus, uveitis, or underlying/co-existing retinal disease, are at increased risk of macular oedema during VELSIPITY therapy. It is recommended that patients with a history of diabetes mellitus, uveitis, or retinal disease undergo an ophthalmic evaluation prior to treatment initiation with VELSIPITY and have follow-up evaluations while receiving therapy.

Patients who present with visual symptoms of macular oedema should be evaluated and, if confirmed, treatment with etrasimod should be discontinued. A decision on whether or not VELSIPITY should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Malignancies

Cases of malignancies (including skin malignancies) have been reported in patients treated with S1P receptor modulators. If a suspicious skin lesion is observed, it should be promptly evaluated. 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. Patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving other S1P receptor modulators. Such events have not been reported for VELSIPITY-treated patients in the development programme. Should a VELSIPITY-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 ischaemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with VELSIPITY should be discontinued.

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 VELSIPITY (see Section 5.1). VELSIPITY should be used with caution in patients with severe respiratory disease (i.e., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease).

4.5. Interaction with other medicinal products and other forms of interaction

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, OCT1/2 transporters. Drugs that are inhibitors of these transporters are unlikely to impact the pharmacokinetics of etrasimod.

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 increases the exposure of etrasimod. Co-administration with VELSIPITY and such agents (e.g., fluconazole) is not recommended.

CYP2C8, CYP2C9, and CYP3A4 inducers
The co-administration of etrasimod with rifampin (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 of the main metabolising CYPs (CYP2C8, CYP2C9, and CYP3A4) decreases the exposure of etrasimod. Co-administration with VELSIPITY and such agents (e.g., rifampin) is not recommended.

Effect of CYP2C9 polymorphism

Due to the potential for increased exposure of etrasimod, co-administration of etrasimod in patients who are known or suspected to be CYP2C9 poor metabolisers (<5% of the population) and who take medicinal products that are moderate or strong inhibitors of CYP2C8 and/or CYP3A4 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 Section 4.4).

Because of the potential additive effects on heart rate, if treatment initiation with VELSIPITY is considered in patients on QT prolonging drugs, advice from a cardiologist should be sought (see Section 4.4).

Anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies

VELSIPITY has not been studied in combination with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies. Caution should be used during concomitant administration because of the risk of additive immune system effects during such therapy and in the weeks following administration (see Section 4.4).

Vaccination

Vaccinations may be less effective if administered during and for up to 2 weeks after discontinuation of VELSIPITY treatment. 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 VELSIPITY treatment (see Section 4.4).

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 CYP or membrane transporters.

The strong CYP2C8 inhibitor gemfibrozil increased exposure (AUC) of etrasimod by 36%. This change in exposure is unlikely to be clinically significant.

Oral contraceptives

No clinically significant differences in the pharmacokinetics and pharmacodynamics of oral contraceptive containing 30 mcg ethinyl oestradiol and 150 mcg levonorgestrel were observed when co-administered with etrasimod.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

VELSIPITY is contraindicated in women of childbearing potential not using effective contraception (see Section 4.3). Before initiation of VELSIPITY treatment, a negative pregnancy test result must be available and women of childbearing potential must be counselled on the potential for a serious risk to the foetus and the need for effective contraception during treatment with VELSIPITY (see Pregnancy below).

Because of the time it takes to eliminate the drug from the body after stopping treatment, the potential risk to the foetus may persist and women of childbearing potential should use effective contraception for 10 days after stopping VELSIPITY.

Pregnancy

There are no adequate and well-controlled studies on the developmental risk associated with the use of VELSIPITY in pregnant women.

In animal studies, administration of etrasimod during pregnancy produced adverse effects on development, including embryolethality and foetal malformations, in both rats and rabbits at clinically relevant maternal exposures (see Section 5.3). Based on human experience etrasimod may cause congenital malformations when administered during the first trimester of pregnancy.

VELSIPITY is contraindicated during pregnancy (see Section 4.3). Etrasimod should be stopped at least 10 days before a pregnancy is planned (see Section 4.4). If a woman becomes pregnant during treatment, etrasimod must be immediately discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and follow-up examinations should be performed.

Breastfeeding

It is unknown whether VELSIPITY 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. Etrasimod should not be used during breastfeeding due to the potential risks in nursing infants.

Fertility

The effect of etrasimod on human fertility has not been evaluated. In animal studies, no adverse effects on fertility were observed (see Section 5.3).

4.7. Effects on ability to drive and use machines

VELSIPITY has no or negligible influence on patient’s ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness has been reported (see Section 4.8).

4.8. Undesirable effects

Summary of safety profile

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

Tabulated list of adverse reactions

Table 1: Adverse Drug Reactions (ADRs) By System Organ Class and Council for International Organizations of Medical Science (CIOMS) Frequency Category Listed in Order of Decreasing Medical Seriousness or Clinical Importance Within Each Frequency Category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Infections and infestations		Urinary tract infection[a] Lower respiratory tract infection[b]	
Blood and lymphatic system disorders	Lymphopenia[c*]	Neutropenia[d]	
Metabolism and nutrition disorders		Hypercholesterolaemia[e]	
Nervous system disorders		Headache Dizziness	
Eye disorders		Visual impairment[f]	Macular oedema
Cardiac disorders		Bradycardia[g]	Atrioventricular block[h]
Vascular disorders		Hypertension	
Hepatobiliary disorder		Hepatic enzyme increased[i]	

* Includes additional 365 patients who received etrasimod 2 mg from long-term studies.
[a] Urinary tract infection includes urinary tract infection and cystitis.
[b] Lower respiratory tract infection includes bronchitis and pneumonia.
[c] Lymphopenia includes lymphopenia, lymphocyte count decreased, and lymphocyte percentage decreased.
[d] Neutropenia includes neutropenia and neutrophil count decreased.
[e] Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased.
[f] Visual impairment includes visual impairment, vision blurred, and visual acuity decreased.
[g] Bradycardia includes bradycardia and sinus bradycardia.
[h] Atrioventricular block includes first- or second-degree Mobitz type I.
[i] Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hepatic function abnormal, liver disorder, liver function test abnormal, liver function test increased, and transaminases increased.

Description of selected adverse reactions

Bradyarrhythmia
In ELEVATE UC 52, bradycardia was reported on the day of treatment initiation in 1.0% of 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 ELEVATE UC 12, bradycardia was reported on the day of treatment initiation in 2.1% of 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 0.7% of VELSIPITY-treated patients compared to none in placebo in ELEVATE UC 52 and in 0.4% of VELSIPITY-treated patients compared to none in placebo in ELEVATE UC 12; however, in ELEVATE UC 52 and ELEVATE UC 12, Mobitz type II second- or third-degree AV blocks were not reported in patients treated with VELSIPITY.

Infections
In ELEVATE UC 52, the overall rate of infections and rate of serious infections in patients treated with VELSIPITY was comparable to that in patients who received placebo (24.9% vs 22.2%, and 1.0% vs 3.5%, respectively). In ELEVATE UC 12, the overall rate of infections and rate of serious infections in patients treated with VELSIPITY was comparable to that in patients who received placebo (11.3% vs 12.1%, and none in both groups, respectively). The most common adverse reaction for infections was urinary tract infection.

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 ELEVATE UC 12. These events did not lead to treatment discontinuation.

Elevated hepatic enzymes
In ELEVATE UC 52, elevations of alanine aminotransferase (ALT) to 5-fold the upper limit of normal (ULN) or greater occurred in 0.7% of patients treated with VELSIPITY and 0.7% of patients who received placebo, and in ELEVATE UC 12 elevations occurred in 0.8% of 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 4.5% of patients treated with VELSIPITY and 0.7% of patients who received placebo, and in ELEVATE UC 12 elevations occurred in 2.5% of 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.

Overall, the percentage of discontinuation because of elevations in hepatic enzymes was 0.4% in patients treated with VELSIPITY, and 0.4% in patients who received placebo.

Increased blood pressure
In ELEVATE UC 52 and ELEVATE UC 12, 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. Hypertension was reported as an adverse reaction in 2.1% of patients treated with VELSIPITY and in 1.0% of patients who received placebo. The majority of the events were mild to moderate in severity.

Macular oedema
In ELEVATE UC 52, macular oedema was reported in 0.3% of patients treated with VELSIPITY and in no patients receiving placebo. In ELEVATE UC 12, macular oedema was reported in 0.4% of patients treated with VELSIPITY and in 0.9% of patients receiving placebo.

Herpes viral infections
Cases of localised herpes viral infection were seen with S1P receptor modulators, including VELSIPITY. In ELEVATE UC 52, herpes zoster was reported in 0.7% of patients treated with VELSIPITY and in none of the patients who received placebo. In ELEVATE UC 12, herpes zoster was reported in none of the patients treated with VELSIPITY and in 1.7% of patients who received placebo.

4.9. Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action

Etrasimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1, 4 and 5 ($S1P_{1,4,5}$) and is a balanced G-protein and beta-arrestin agonist at $S1P_1$. Etrasimod has no activity on $S1P_2$ or $S1P_3$. 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.

Pharmacodynamic effects

Heart rate and rhythm
VELSIPITY may result in a transient decrease in heart rate and AV conduction upon treatment initiation (see Section 4.4). On Day 1, in UC patients from ELEVATE UC 52 and ELEVATE UC 12, the greatest mean decrease in heart rate was observed at Hour 2 or 3 post-dose.

Effect on QT interval
In a thorough QT study, daily administration of etrasimod doses 2 mg (recommended dose) to 4 mg (two times recommended dose) were evaluated in healthy subjects. Etrasimod did not cause a QTc prolongation to any clinically relevant extent under the conditions (doses/regimens) evaluated in the study. Etrasimod C_{max} after 4 mg was approximately 1.4-fold to 1.6-fold higher than after 2 mg.

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 10^9/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.

Pulmonary function
Reductions in FEV_1 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 FEV_1 in patients treated with VELSIPITY 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 VELSIPITY 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 FEV_1/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.

Clinical efficacy and safety

The efficacy of VELSIPITY was evaluated in 2 randomised, 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.

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.

ELEVATE UC 52

ELEVATE UC 52 was a treat-through study, with a total of 433 patients randomised 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, and 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, mucosal healing, 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 2).

A significantly greater proportion of patients treated with VELSIPITY achieved clinical remission, endoscopic improvement, symptomatic remission, and mucosal healing at Week 12 and at Week 52, corticosteroid-free clinical remission and sustained clinical remission at Week 52, compared to placebo (see Table 2).

Table 2: 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]	**10**	**7%**	**74**	**27%**	**20% (13%, 27%)[i]**
No prior biologic/ JAK inhibitor exposure	9/93	10%	60/194	31%	
Prior biologic/ JAK inhibitor exposure	1/42	2%	14/80	18%	
Endoscopic Improvement[c]	**19**	**14%**	**96**	**35%**	**21% (13%, 29%)[i]**
No prior biologic/ JAK inhibitor exposure	17/93	18%	76/194	39%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	20/80	25%	
Symptomatic Remission[d]	**29**	**22%**	**126**	**46%**	**25% (15%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	22/93	24%	101/194	52%	
Prior biologic/ JAK inhibitor exposure	7/42	17%	25/80	31%	
Mucosal Healing[e]	**6**	**4%**	**58**	**21%**	**17% (11%, 23%)[i]**
No prior biologic/ JAK inhibitor exposure	6/93	7%	47/194	24%	
Prior biologic/ JAK inhibitor exposure	0/42	0%	11/80	14%	
Clinical Response[f]	**46**	**34%**	**171**	**62%**	**28% (19%, 38%)[i]**
No prior biologic/ JAK inhibitor exposure	35/93	38%	132/194	68%	
Prior biologic/ JAK inhibitor exposure	11/42	26%	39/80	49%	
Week 52 Endpoints					
Clinical Remission[b]	**9**	**7%**	**88**	**32%**	**25% (18%, 32%)[i]**
No prior biologic/ JAK inhibitor exposure	7/93	8%	71/194	37%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	17/80	21%	

	Placebo N = 135		VELSIPITY N = 274		Treatment Difference (95% CI)[a]
	n	%	n	%	
Endoscopic Improvement[c]	**14**	**10%**	**102**	**37%**	**27% (19%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	12/93	13%	78/194	40%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	24/80	30%	
Symptomatic Remission[d]	**25**	**19%**	**119**	**43%**	**25% (16%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	19/93	20%	97/194	50%	
Prior biologic/ JAK inhibitor exposure	6/42	14%	22/80	28%	
Mucosal Healing[e]	**11**	**8%**	**73**	**27%**	**18% (11%, 25%)[i]**
No prior biologic/ JAK inhibitor exposure	10/93	11%	55/194	28%	
Prior biologic/ JAK inhibitor exposure	1/42	2%	18/80	23%	
Clinical Response[f]	**31**	**23%**	**132**	**48%**	**25% (16%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	25/93	27%	103/194	53%	
Prior biologic/ JAK inhibitor exposure	6/42	14%	29/80	36%	
Corticosteroid-free Clinical Remission[g]	**9**	**7%**	**88**	**32%**	**25% (18%, 32%)[i]**
No prior biologic/ JAK inhibitor exposure	7/93	8%	71/194	37%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	17/80	21%	
Sustained Clinical Remission[h]	**3**	**2%**	**49**	**18%**	**16% (11%, 21%)[i]**
No prior biologic/ JAK inhibitor exposure	2/93	2%	41/194	21%	
Prior biologic/ JAK inhibitor exposure	1/42	2%	8/80	10%	

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] Mucosal healing 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).

	Placebo N = 135		VELSIPITY N = 274		Treatment Difference (95% CI)[a]
	n	%	n	%	

[f] Clinical response was defined as a ≥2-point and ≥30% decrease from baseline in mMS, and a ≥1-point decrease from baseline in RB subscore or an absolute RB subscore ≤1.
[g] Corticosteroid-free clinical remission was defined as clinical remission at Week 52 without receiving corticosteroids for at least 12 weeks prior to Week 52.
[h] Sustained clinical remission was defined as clinical remission at both Week 12 and Week 52.
[i] p <0.001

Supplementary analysis of mMS 4 to 9
Consistent with the primary analysis (mMS of 5 to 9 including ES ≥2 and RB subscore ≥1), a greater proportion of patients with mMS of 4 to 9 (including ES ≥2 and RB subscore ≥1) treated with VELSIPITY compared to placebo achieved clinical remission (28% vs 8%, 2-sided p-value <0.001), endoscopic improvement (37% vs 17%, 2-sided p-value <0.001), symptomatic remission (46% vs 22%, 2-sided p-value <0.001), and mucosal healing (23% vs 6%, 2-sided p-value <0.001) at Week 12, clinical remission (33% vs 8%, 2-sided p-value <0.001), endoscopic improvement (39% vs 13%, 2-sided p-value <0.001), symptomatic remission (44% vs 19%, 2-sided p-value <0.001), mucosal healing (27% vs 10%, 2-sided p-value <0.001), corticosteroid-free clinical remission (33% vs 7%, 2-sided p-value <0.001), and sustained clinical remission (19% vs 3%, 2-sided p-value <0.001) at 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 (46% vs 29%) and Week 52 (42% vs 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%).

Complete symptomatic remission
Complete symptomatic remission was defined as a SF subscore of 0 and RB subscore of 0. At Week 4, a greater proportion of patients treated with VELSIPITY compared to placebo achieved complete symptomatic remission (11% vs 4%).

Stool frequency and rectal bleeding subscores
Decreases in SF and RB subscores were observed as early as Week 2 in patients treated with VELSIPITY compared to placebo.

Cessation of rectal bleeding
A greater proportion of patients achieved an RB subscore of 0 as early as Week 4 with VELSIPITY compared with placebo (44% vs 27%).

Endoscopic and histologic assessment
Normalisation of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. A greater proportion of patients 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 2%).

Endoscopic remission and Geboes histologic score <2.0 (indicating no neutrophils in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations, or granulation tissue) were achieved by a greater proportion of patients treated with VELSIPITY compared to placebo at Week 12 (11% vs 2%) and at Week 52 (18% vs 5%).

When defined as ES ≤1 and Geboes ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue), a greater proportion of patients treated with VELSIPITY compared to placebo achieved histologic-endoscopic mucosal improvement at Week 12 (31% vs 10%) and Week 52 (40% vs 11%).

Abdominal pain and bowel urgency
At Week 12, a greater proportion of patients treated with VELSIPITY compared to placebo had absence of abdominal pain (27% vs 13%) and absence of bowel urgency (19% vs 7%). At Week 52, a greater proportion of patients treated with VELSIPITY compared to placebo had absence of abdominal pain (22% vs 7%) and absence of bowel urgency (19% vs 8%).

Inflammatory bowel disease questionnaire (IBDQ)
Patients treated with VELSIPITY compared to placebo demonstrated greater improvement from baseline in the total and all 4 domain scores of the IBDQ (bowel symptoms, systemic function, emotional function, and social function) at Week 12 and at Week 52.

ELEVATE UC 12

In ELEVATE UC 12, a total of 354 patients were randomised 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 subjects achieving endoscopic improvement, symptomatic remission, mucosal healing, and clinical response 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 3).

A significantly greater proportion of patients treated with VELSIPITY achieved clinical remission, endoscopic improvement, symptomatic remission, and mucosal healing compared to placebo at Week 12 (see Table 3).

Table 3: Proportion of Patients Meeting Efficacy Endpoints at Week 12 in ELEVATE UC 12

	Placebo N = 112		VELSIPITY N = 222		Treatment Difference (95% CI)[a]
	n	%	n	%	
Clinical Remission[b]	**17**	**15%**	**55**	**25%**	**10% (1%, 18%)[g]**
No prior biologic/ JAK inhibitor exposure	12/74	16%	41/148	28%	
Prior biologic/ JAK inhibitor exposure	5/38	13%	14/74	19%	
Endoscopic Improvement[c]	**21**	**19%**	**68**	**31%**	**12% (3%, 21%)[g]**
No prior biologic/ JAK inhibitor exposure	14/74	19%	51/148	35%	
Prior biologic/ JAK inhibitor exposure	7/38	18%	17/74	23%	
Symptomatic Remission[d]	**33**	**30%**	**104**	**47%**	**17% (7%, 28%)[g]**
No prior biologic/ JAK inhibitor exposure	23/74	31%	73/148	49%	
Prior biologic/ JAK inhibitor exposure	10/38	26%	31/74	42%	
Mucosal Healing[e]	**10**	**9%**	**36**	**16%**	**7% (1%, 14%)[g]**
No prior biologic/ JAK inhibitor exposure	8/74	11%	28/148	19%	
Prior biologic/ JAK inhibitor exposure	2/38	5%	8/74	11%	
Clinical Response[f]	**46**	**41%**	**138**	**62%**	**21% (10%, 32%)[h]**
No prior biologic/ JAK inhibitor exposure	32/74	43%	97/148	66%	
Prior biologic/ JAK inhibitor exposure	14/38	37%	41/74	55%	

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] Mucosal healing 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] Clinical response was defined as a ≥2-point and ≥30% decrease from baseline in mMS, and a ≥1-point decrease from baseline in RB subscore or an absolute RB subscore ≤1.

[g] $p < 0.05$.

[h] $p < 0.001$.

Supplementary analysis of mMS 4 to 9
Consistent with the primary analysis (mMS of 5 to 9 including ES ≥2 and RB subscore ≥1), a greater proportion of patients with mMS of 4 to 9 (including ES ≥2 and RB subscore ≥1) treated with VELSIPITY compared to placebo achieved clinical remission (26% vs 15%, 2-sided p-value = 0.007), endoscopic improvement (33% vs 19%, 2-sided p-value = 0.002), symptomatic remission (48% vs 29%, 2-sided p-value <0.001), and mucosal healing (17% vs 9%, 2-sided p-value = 0.012) at Week 12.

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

Complete symptomatic remission
Complete symptomatic remission was defined as a SF subscore of 0 and RB subscore of 0. At Week 4, a greater proportion of patients treated with VELSIPITY compared to placebo achieved complete symptomatic remission (12% vs 4%).

Stool frequency and rectal bleeding subscores
Decreases in SF and RB subscores were observed as early as Week 2 in patients treated with VELSIPITY compared to placebo.

Cessation of rectal bleeding
A greater proportion of patients achieved an RB subscore of 0 as early as Week 4 with VELSIPITY compared with placebo (47% vs 25%).

Endoscopic and histologic assessment
Normalisation of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. A greater proportion of patients treated with VELSIPITY compared to placebo achieved endoscopic remission by Week 12 (17% vs 8%).

Endoscopic remission and Geboes histologic score <2.0 (indicating no neutrophils in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations, or granulation tissue) were achieved by a greater proportion of patients treated with VELSIPITY compared to placebo at Week 12 (10% vs 5%).

When defined as ES ≤1 and Geboes ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue), a greater proportion of patients treated with VELSIPITY compared to placebo achieved histologic-endoscopic mucosal improvement at Week 12 (29% vs 12%).

Abdominal pain and bowel urgency
At Week 12, a greater proportion of patients treated with VELSIPITY compared to placebo had absence of abdominal pain (32% vs 18%) and absence of bowel urgency (21% vs 12%).

Inflammatory bowel disease questionnaire (IBDQ)
Patients treated with VELSIPITY compared to placebo demonstrated greater improvement from baseline in the total and all 4 domain scores of the IBDQ (bowel symptoms, systemic function, emotional function, and social function) at Week 12.

5.2. Pharmacokinetic properties

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.

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 faeces (11.2% of administered radioactive dose). Steady state exposure was reached within 7 days of dose initiation of etrasimod.

Effect of food
Food intake can result in 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, VELSIPITY can be administered without regard to meals.

Distribution

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

Elimination

After oral administration, the apparent steady state oral clearance (CL/F) was approximately 1 L/h. The mean plasma elimination half-life ($t_{1/2}$) of etrasimod is approximately 30 hours.

Metabolism
Etrasimod is extensively metabolised via CYP2C8 (38%), CYP2C9 (37%), and CYP3A4 (22%), and with minor contribution via CYP2C19 and CYP2J2. Unchanged etrasimod is the main circulating component in plasma. Etrasimod is extensively metabolised by oxidation, dehydrogenation, and conjugation by UGTs and sulfotransferases.

Excretion
Etrasimod is primarily eliminated hepatically with 82% recovery of total radioactive dose in the faeces and 4.89% in the urine. Unchanged etrasimod was only detected in faeces, but not in urine.

Special populations

Male and female patients
Sex or weight have no clinically significant influence on etrasimod pharmacokinetics.

Racial or ethnic groups
No clinically relevant pharmacokinetic differences were observed between Japanese, Chinese, and Caucasian subjects.

Paediatric population
The safety and efficacy of VELSIPITY in children and adolescents have not been established.

Elderly
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.

Renal impairment
No dose adjustments are needed in patients with renal impairment as C_{max} 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 haemodialysis on the pharmacokinetics of etrasimod was not evaluated.

Hepatic impairment
Etrasimod is contraindicated in patients with severe hepatic impairment. No dose adjustments are needed in patients with mild or moderate hepatic impairment. The total etrasimod AUC parameters 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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated-dose toxicity. Changes in the dog heart (hypertrophy/ hyperplasia of the tunica media of left ventricular arteries) were observed in 3- and 9-month repeated-dose toxicity studies at exposures ≥24 times the recommended human dose (RHD) based on AUC; however, the relevance for humans is not known.

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 haemangioma at 6 and 20 mg/kg/day in males and females. Systemic exposure at the lowest-observed-effect level of 6 mg/kg/day was approximately 42 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 tumours. 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.

Mutagenesis

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

Impairment of fertility

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.

Reproductive toxicity

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 foetuses 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. Maternal plasma AUC at the lowest dose tested 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, post-implantation loss with a corresponding number of viable foetuses was observed at 10 and 20 mg/kg/day. Etrasimod-related foetal visceral and/or skeletal variations were noted at 10 and 20 mg/kg/day. There were no effects on embryofoetal development at 2 mg/kg/day. Maternal plasma exposure (AUC) at the no-adverse-effect 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 decreased mean pup weights at all dose levels during the pre-weaning period, lower pup viability at 2 and 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 neurobehavioural function in offspring at any dose level tested. Plasma exposure (AUC) in dams at the lowest dose tested 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

VELSIPITY tablets contain the following inactive ingredients:

- Magnesium stearate

- Mannitol
- Microcrystalline cellulose
- Sodium starch glycolate

The green film 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 hydrolysed)
- Talc
- Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Refer to outer carton.

6.4. Special precautions for storage

Store in the original package, in order to protect from moisture.

6.5. Nature and contents of container

30 count 100 mL high-density polyethylene (HDPE) bottle closed with a polypropylene cap, desiccant integrated directly into the cap.

Packs of 28 (2 x 14) or 98 (7 x 14) aluminum blister strip laminated to an oriented polyamine (oPA) film and integrated desiccant layer (HDPE/LDPE), with a paper/aluminum/LDPE backing.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Pfizer Inc.
New York,
United States