1. NAME OF THE MEDICINAL PRODUCT

Velsipity

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect

Each film-coated tablet contains 0.0156 mg of the colouring agent tartrazine (E102).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

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

Patient/Caregiver Safety Information Guide and Pregnancy Reminder Card
The marketing of Velsipity is subject to a risk management plan (RMP) including a ‘Patient/Caregiver Safety Information Guide’ and ‘Pregnancy Reminder card’ for patients. The ‘Patient safety information Guide’ and ‘Pregnancy Reminder Card’, emphasize important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the Guide and Card before starting treatment.

Prescriber’s Checklist
This product is marketed with a prescriber’s checklist providing important safety information. Please ensure you are familiar with this material as it contains important safety information

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Velsipity is indicated for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent.

4.2 Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the management of ulcerative colitis.

Posology

The recommended dose is 2 mg etrasimod taken once daily.

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 (see section 5.2).

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. Etrasimod should not be used in patients with severe hepatic impairment (see sections 4.3 and 5.2).

Paediatric population
The safety and efficacy of etrasimod in children and adolescents less than 16 years of age have not yet been established. No data are available.

Given the limited data in adolescents aged 16 and over, etrasimod should be used with caution especially when body weight is less than 40 kg due to the potential for increase in exposure (see section 5.2).

Method of administration

Oral use.

It is recommended that etrasimod be administered with food for the first 3 days to attenuate potential transient heart rate lowering effects related to initiation of treatment (see section 4.4). Etrasimod can then be taken with or without food (see section 5.2).

Tablets should be swallowed whole with water and not be split, crushed or chewed because these methods have not been studied in clinical trials.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Immunodeficient state (see section 4.4).
- Patients who in the last 6 months experienced 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 history or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless patient has a functioning pacemaker.
- Severe active infections, active chronic infections such as hepatitis or tuberculosis (see section 4.4).

- Active malignancies.
- Severe hepatic impairment.
- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Bradyarrhythmia and atrioventricular conduction delays

Treatment initiation with etrasimod
Prior to treatment initiation with etrasimod, an electrocardiogram (ECG) should be obtained in all patients to assess for pre-existing cardiac abnormalities. In patients with certain pre-existing conditions, first dose monitoring is recommended (see below). When reinitiating 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 etrasimod may result in a transient decrease in heart rate and AV conduction delays (see sections 4.8 and 5.1).

Caution should be applied when etrasimod is initiated in patients receiving treatment with a beta-blocker because of the potential additive effects on lowering heart rate. Similar caution should be applied if patients receive calcium channel blockers, QT prolonging medicinal products, Class Ia and Class III anti-arrhythmic substances (see section 4.5), since co-administration of these substances with etrasimod may lead to additive effects.

Temporary interruption of beta-blocker treatment may be needed prior to initiation of etrasimod, depending on the resting HR before initiation of etrasimod (see also section below and section 4.5). If interruption is deemed necessary, treatment with a beta-blocker can be reinitiated depending on the time of reaching the baseline heart rate. Beta-blocker treatment can be initiated in patients receiving stable doses of etrasimod.

Cardiologist advice should be obtained before initiation of etrasimod to determine overall benefit risk and the most appropriate monitoring strategy in patients with the following conditions:
- Significant QT prolongation (QTcF ≥ 450 msec in males, ≥ 470 msec in females).
- Arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic medicinal products.
- Unstable ischaemic heart disease, history of cardiac arrest, cerebrovascular disease (occurring more than 6 months prior to treatment initiation), or uncontrolled hypertension.
- History of symptomatic bradycardia, recurrent cardiogenic syncope, or severe untreated sleep apnoea.

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 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.

Infections

Risk of infections
Etrasimod causes a mean reduction in peripheral blood lymphocyte count ranging from 43 to 55% of baseline values over 52 weeks because of reversible sequestration of lymphocytes in lymphoid tissues (see section 5.1). Etrasimod may, therefore, increase the susceptibility to infections (see section 4.8).

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

Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts < 0.2 x 10^9/L, if confirmed, should lead to interruption of etrasimod therapy until the level reaches > 0.5 x 10^9/L when re-initiation of etrasimod can be considered (see section 4.2).

The initiation of etrasimod in patients with any active infection should be delayed until the infection is resolved (see section 4.3).

Patients should be instructed to promptly report symptoms of infection to their physician. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy.

If a patient develops a serious infection, interruption of etrasimod should be considered.

As residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist up to 2 weeks after discontinuation of etrasimod, vigilance for infection should be continued throughout this period (see section 5.1).

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.

PML has been reported in multiple sclerosis patients treated with 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.

Prior and concomitant treatment with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies
In clinical studies, 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 clinical studies, concomitant use of corticosteroids was allowed; however, long-term data on concomitant use of etrasimod and corticosteroids are limited (see section 5.1).

Caution should be used when co-administering etrasimod and anti-neoplastic, immune-modulating, or immunosuppressive (including corticosteroid) therapies to patients, because of the risk of additive immune system effects during such therapy (see section 4.5).

When switching to etrasimod from immunosuppressive therapies, the duration of effects and mechanism of action should be considered to avoid unintended additive immune system effects. An appropriate washout period may need to be applied.

Vaccinations
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 immunisations are required, these should be administered at least 4 weeks prior to initiation of etrasimod. The use of live attenuated vaccines during and for at least 2 weeks after treatment with etrasimod should be avoided (see section 5.1).

It is recommended to update immunisations in agreement with current immunisation guidelines prior to initiating etrasimod therapy.

Liver injury

Elevations of aminotransferases may occur in patients receiving etrasimod (see section 4.8). Recent transaminase and bilirubin levels (i.e., within last 6 months) should be available before initiation of treatment with etrasimod.

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. Etrasimod should be discontinued if significant liver injury is confirmed (for example, alanine aminotransferase (ALT) exceeds 3-fold the upper limit of normal (ULN) and total bilirubin exceeds 2-fold the ULN).

Resumption of therapy will be dependent on whether another cause of liver injury is determined and on the benefits to patient of resuming etrasimod therapy versus the risks of recurrence of liver dysfunction. Although there are no data to establish that patients with pre-existing liver disease are at increased risk of developing elevated liver function test values when taking etrasimod, caution should be exercised in patients with a history of significant liver disease.

Increased blood pressure

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

Women of childbearing potential

Based on animal studies, etrasimod may cause foetal harm (see sections 4.6 and 5.3). Due to the risk to the foetus, etrasimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception (see sections 4.3 and 4.6). Before initiation of treatment, women of childbearing potential must be informed about this risk to the foetus, must have a negative pregnancy test, and must use effective contraception during treatment and for at least 14 days after treatment discontinuation (see section 4.6).

Macular oedema

S1P receptor modulators, including etrasimod, have been associated with an increased risk of macular oedema. Macular oedema with or without visual symptoms has been reported in 0.3% of patients treated with Velsipity.

Patients with a history of diabetes mellitus, uveitis, and/or underlying/co-existing retinal disease, are at increased risk of macular oedema during etrasimod therapy (see section 4.8). It is recommended that these patients undergo an ophthalmic evaluation prior to treatment initiation with etrasimod and have follow-up evaluations while receiving therapy.

In patients without the risk factors above, an ophthalmic evaluation of the fundus, including the macula, is recommended within 3-4 months after starting etrasimod treatment (cases reported with etrasimod occurred within this timeframe) and at any time if there is a change in vision while taking etrasimod.

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 etrasimod should be re-initiated after resolution needs to take into account the potential benefits and risks for the individual patient.

Malignancies

Cases of malignancies (including cutaneous malignancies) have been reported in patients treated with S1P receptor modulators. If a suspicious skin lesion is observed, it should be promptly evaluated.

Since there is a potential risk of malignant skin growths, patients treated with etrasimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Posterior reversible encephalopathy syndrome (PRES)

Rare cases of PRES have been reported in patients receiving S1P receptor modulators. 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 ischaemic 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.

Interaction with other medicinal products, CYP2C9 polymorphism

Etrasimod should not be co-administered with a therapeutic agent or a combination of agents that are moderate to strong inhibitors of two or more of the following CYP enzymes (CYP2C8, CYP2C9, and CYP3A4) due to the risk of increased exposure to etrasimod (see section 4.5).

The use of etrasimod is not recommended when co-administered with a therapeutic agent or a combination of agents that are moderate to strong inducers of two or more of the following CYP enzymes (CYP2C8, CYP2C9, and CYP3A4) due to the risk of decreased exposure to etrasimod (see section 4.5).

The use of etrasimod is not recommended 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 due to the risk of increased exposure of etrasimod (see section 4.5).

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. Etrasimod should be used with caution in patients with severe respiratory disease (e.g., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease).

Excipients

Tartrazine
This medicinal product contains tartrazine (E102) which may cause allergic reactions.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of inhibitors of CYP2C8, CYP2C9, and CYP3A4 on etrasimod

The co-administration of etrasimod with steady state fluconazole (moderate CYP2C9 and CYP3A4 inhibitor) increased exposure (AUC) of etrasimod by 84%. Co-administration of etrasimod with a therapeutic agent or a combination of agents that are moderate to strong inhibitors of two or more of the following CYP enzymes (CYP2C8, CYP2C9, and CYP3A4) (e.g., fluconazole) increases the exposure of etrasimod and is not recommended (see section 4.4).

Effect of inducers of CYP2C8, CYP2C9, and CYP3A4 on etrasimod

The co-administration of etrasimod with rifampicin (strong CYP3A4, moderate CYP2C8, and CYP2C9 inducer) decreased exposure (AUC) of etrasimod by 49%. Co-administration of etrasimod with a therapeutic agent or a combination of agents that are moderate to strong inducers of two or more of the following CYP enzymes (CYP2C8, CYP2C9, and CYP3A4) (e.g., rifampicin, enzalutamide) decreases the exposure of etrasimod and is not recommended (see section 4.4).

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 (see section 4.4).

Beta blockers and calcium channel blockers

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

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

Caution is recommended for patients receiving medicinal products that slow heart rate or atrioventricular conduction because of the potential additive effects on lowering heart rate (see section 4.4).

Anti-arrhythmic medicinal products, QT prolonging medicinal products, medicinal products that may decrease heart rate

Etrasimod has not been studied in patients taking QT prolonging medicinal products.

Class Ia (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) anti-arrhythmic medicinal products have been associated with cases of Torsades de Pointes in patients with bradycardia. If treatment with etrasimod is considered in patients on Class Ia or Class III anti-arrhythmic medicinal products, advice from a cardiologist should be sought (see section 4.4).

Due to the potential additive effects on heart rate, if treatment initiation with etrasimod is considered in patients on QT prolonging medicinal products, advice from a cardiologist should be sought (see section 4.4).

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

Etrasimod 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 treatment with etrasimod. The use of live attenuated vaccine may carry the risk of infection and should therefore be avoided during etrasimod treatment and for at least 2 weeks after discontinuation of treatment with etrasimod (see section 4.4).

Oral contraceptives

No clinically significant differences in the pharmacokinetics and pharmacodynamics of an oral contraceptive containing 30 mcg ethinyl oestradiol and 150 mcg levonorgestrel were observed when co-administered with etrasimod. Co-administration of etrasimod with an oral contraceptive containing ethinyl oestradiol and levonorgestrel increases AUC values of the ethinyl oestradiol and levonorgestrel by approximately 24% and 32%, respectively.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Velsipity is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the foetus. Due to the time it takes to eliminate etrasimod from the body after stopping treatment, the potential risk to the foetus may persist and women of childbearing potential must use effective contraception during etrasimod treatment and for at least 14 days after treatment discontinuation (see section 4.4).

Specific measures are also included in the Healthcare Professional checklist. These measures must be implemented before etrasimod is prescribed to female patients and during treatment.

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Pregnancy

There is a limited amount of data from the use of etrasimod in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Clinical experience with another sphingosine-1-phosphate receptor modulator indicated a 2-fold higher risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population. Based on human experience etrasimod may cause congenital malformations when administered during the first trimester of pregnancy. The limited human data available for etrasimod also suggest an increased risk of abnormal pregnancy outcomes. Consequently, Velsipity is contraindicated during pregnancy (see section 4.3).

Etrasimod should be stopped at least 14 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.

Breast-feeding
It is unknown whether etrasimod is excreted in human milk. A study in lactating rats has indicated excretion of etrasimod in milk (see section 5.3). A risk to newborns/infants cannot be excluded. Etrasimod should not be used during breast-feeding.

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

Etrasimod has no or negligible influence on the ability to drive and use machines.

However, patients who experience dizziness after taking etrasimod should refrain from driving or using machines until the dizziness resolves (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The adverse reactions observed in patients treated with etrasimod are listed below by system organ class (SOC) and frequency category. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000).

Table 1: Adverse reactions

System organ class (SOC)	Very common	Common	Uncommon
Infections and infestations		Urinary tract infection[a], lower respiratory tract infection[b]	
Blood and lymphatic system disorders	Lymphopenia[c]	Neutropenia	
Metabolism and nutrition disorders		Hypercholesterolaemia[d]	
Nervous system disorders		Headache, dizziness	
Eye disorders		Visual impairment	Macular oedema
Cardiac disorders		Bradycardia[e]	Atrioventricular block[f]
Vascular disorders		Hypertension	
Hepatobiliary disorders		Hepatic enzyme increased	

[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] Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased.
[e] Bradycardia includes bradycardia and sinus bradycardia. See "Description of selected adverse reactions" below.
[f] Atrioventricular block includes first- or second-degree Mobitz type I. See "Description of selected adverse reactions" below.

Description of selected adverse reactions

Bradyarrhythmia
In ELEVATE UC 52 and ELEVATE UC 12, bradycardia was reported as an AE on the day of treatment initiation in 1.5% of patients treated with etrasimod. On Day 2, bradycardia was reported as an AE in 0.4% of patients treated with etrasimod. Bradycardia was recorded more frequently on ECG monitoring (see section 5.1).

In ELEVATE UC 52 and ELEVATE UC 12, on the day of treatment initiation, events of first- or second-degree Mobitz type I AV blocks were reported as an AE in 0.6% of patients treated with etrasimod. Events of AV block were mostly transient and asymptomatic. PR interval prolongation was recorded more frequently on ECG monitoring (see section 5.1).

Infections
In ELEVATE UC 52 and ELEVATE UC 12, the overall rate of infections and rate of serious infections in patients treated with etrasimod was comparable to that in patients who received placebo (18.8% vs 17.7% and 0.6% vs 1.9%, respectively). Etrasimod increased the risk of urinary tract infections and lower respiratory tract infections (see Table 1).

Blood lymphocyte count and neutrophil count reduction
Etrasimod partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood (see section 5.1). The proportion of patients treated with etrasimod who experienced lymphocyte counts less than 0.2 x 10^9/L was 3.5% in ELEVATE UC 52 and ELEVATE UC 12. These events did not lead to treatment discontinuation. Etrasimod caused a reversible decrease in neutrophil count; the proportion of patients treated with etrasimod who experienced neutrophil counts less than 0.5 x 10^9/L was 0.2% in ELEVATE UC 52 and ELEVATE UC 12. These events did not lead to treatment discontinuation.

Elevated hepatic enzymes
In ELEVATE UC 52 and ELEVATE UC 12, elevations of ALT to 5-fold and 3-fold the ULN or greater occurred in 0.9% and 4.0% of patients treated with etrasimod, respectively.

The majority (75%) of patients with ALT greater than 3-fold the ULN continued treatment with etrasimod 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 etrasimod.

Hepatic enzyme increased includes events of gamma glutamyl transferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hepatic function abnormal, liver disorder, liver function test abnormal, and transaminases increased (see Table 1).

Increased blood pressure
In ELEVATE UC 52 and ELEVATE UC 12, patients treated with etrasimod 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. 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 etrasimod. All the events were mild to moderate in severity.

Macular oedema
In ELEVATE UC 52 and ELEVATE UC 12, macular oedema was reported in 0.4% of patients treated with etrasimod.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

In patients with overdose of etrasimod, signs and symptoms of bradycardia should be monitored, 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

Pharmacotherapeutic group: Immunosuppressants, sphingosine 1-phosphate (S1P) receptor modulators, etrasimod ATC code: L04AE05

Mechanism of action

Etrasimod is a sphingosine-1-phosphate (S1P) receptor modulator that binds 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 minimal activity on $S1P_3$ and no activity on $S1P_2$. 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 known to be involved in driving UC pathology. Etrasimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance.

Pharmacodynamic effects

Heart rate and rhythm
Etrasimod may result in a transient decrease in heart rate and AV conduction upon treatment initiation (see sections 4.4 and 4.8). On Day 1, in UC patients from ELEVATE UC 52 and ELEVATE UC 12, 33% of subjects had bradycardia (nadir HR below 60 bpm within the first 4 hours), or significant bradycardia in 2.5% (HR nadir below 50 bpm). No patients had HR < 40 bpm following the first dose. The greatest mean decrease in heart rate was observed at Hour 2 or 3 post dose. On Day 1, the mean (SD) change in PR interval from predose to 4 hours post dose with etrasimod was 5.5 msec (18.84). PR interval prolongation > 200 msec was recorded on ECG in 5.1% and higher degree prolongation (> 230 msec) in 1.8% of subjects.

Reduction in blood lymphocyte and neutrophil 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 etrasimod. A reduction in neutrophil counts was observed in controlled clinical studies with etrasimod, mean neutrophil counts were generally in the normal range during etrasimod treatment. Lowered neutrophil counts were maintained on etrasimod treatment and were reversible upon treatment discontinuation.

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.

Clinical efficacy and safety

The efficacy of etrasimod were 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.

Enrolled patients had a modified Mayo score (mMS) of 4 to 9 with an endoscopy score (ES) ≥ 2 and rectal bleeding (RB) subscore ≥ 1. The primary evaluation was based on the population with a mMS of 5 to 9. Patients enrolled across the two studies had a mean age of 40 years with 3 (0.4%) patients less than 18 years of age and 45 (6%) patients 65 years of age or higher; 57% were male, 82% were White, and 13% were Asian.

Patients in these studies may have received the following concomitant UC therapies: 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 etrasimod 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, 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 stool frequency (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).

Of the 433 patients randomised, 91.7% and 86.1% of the patients completed Week 12 in the etrasimod and placebo group, respectively. Beginning with Week 12, patients with no improvement from baseline or who met disease worsening criteria could discontinue per the discretion of the investigator and could continue in the open label extension study. In this treat-through study 55.7% and 31.9% completed Week 52 treatment in the etrasimod and placebo group, respectively.

A significantly greater proportion of patients treated with etrasimod 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		Etrasimod 2 mg N = 274		Treatment difference (95% CI)[a]
	n	%	n	%	
Week 12 endpoints					
Clinical remission[b]	**10**	**7%**	**74**	**27%**	**20% (13%, 27%)[l]**
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%)[l]**
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%)[l]**
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%)[l]**
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%)[l]**
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%)[l]**
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		Etrasimod 2 mg N = 274		Treatment difference (95% CI)[a]
	n	%	n	%	
Endoscopic improvement[c]	**14**	**10%**	**102**	**37%**	**27% (19%, 34%)[l]**
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%)[l]**
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%)[l]**
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%)[l]**
No prior biologic/ JAK inhibitor exposure	25/93	27%	103/194	53%	
Prior biologic/ JAK inhibitor exposure	6/42	14%	29/80	36%	
Sustained clinical remission[g]	**3**	**2%**	**49**	**18%**	**16% (11%, 21%)[l]**
No prior biologic/ JAK inhibitor exposure	2/93	2%	41/194	21%	
Prior biologic/ JAK inhibitor exposure	1/42	2%	8/80	10%	
Corticosteroid-free clinical remission[h]	**9**	**7%**	**88**	**32%**	**25% (18%, 32%)[l]**
No prior biologic/ JAK inhibitor exposure	7/93	8%	71/194	37%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	17/80	21%	
Corticosteroid-free clinical remission among patients treated with corticosteroids at baseline[i]	3/40	8%	27/87	31%	**23% (10%, 36%)[l]**
No prior biologic/ JAK inhibitor exposure	2/26	8%	22/59	37%	
Prior biologic/ JAK inhibitor exposure	1/14	7%	5/28	18%	

	Placebo N = 135		Etrasimod 2 mg N = 274		Treatment difference (95% CI)[a]
	n	%	n	%	
Corticosteroid-free symptomatic remission[j]	25	19%	119	43%	**25% (16%, 34%)[l]**
No prior biologic/ JAK inhibitor exposure	19/93	20%	97/194	50%	
Prior biologic/ JAK inhibitor exposure	6/42	14%	22/80	28%	
Corticosteroid-free endoscopic improvement[k]	14	10%	101	37%	**26% (19%, 34%)[l]**
No prior biologic/ JAK inhibitor exposure	12/93	13%	78/194	40%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	23/80	29%	

[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] Sustained clinical remission was defined as clinical remission at both Week 12 and Week 52.
[h] Corticosteroid-free clinical remission was defined as clinical remission at Week 52 without receiving corticosteroids for at least 12 weeks immediately prior to Week 52.
[i] Corticosteroid-free clinical remission among patients treated with corticosteroids at baseline was defined as clinical remission at Week 52 without receiving corticosteroids for at least 12 weeks immediately prior to Week 52 among patients treated with corticosteroids at baseline.
[j] Corticosteroid-free symptomatic remission was defined as SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline) and RB subscore of 0 for at least 12 weeks immediately prior to Week 52.
[k] Corticosteroid-free endoscopic improvement was defined as ES ≤ 1 (excluding friability) for at least 12 weeks immediately prior to Week 52.
[l] $p < 0.001$.

Supplementary analysis of mMS 4
The efficacy results in patients with mMS of 4 (including ES ≥ 2 and RB subscore ≥ 1) were consistent with those of the primary analysis.

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

Early onset of symptomatic improvement
At Week 2 (first study visit), a greater proportion of patients treated with etrasimod compared to placebo achieved symptomatic remission (16% vs 11%). At Week 4, a greater proportion of patients

treated with etrasimod compared to placebo achieved complete symptomatic remission (11% vs 4%) defined as a SF subscore of 0 and RB subscore of 0.

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 etrasimod 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 etrasimod compared to placebo at Week 12 (11% vs 2%) and at Week 52 (18% vs 5%).

Abdominal pain and bowel urgency
At Week 12, a greater proportion of patients treated with etrasimod 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 etrasimod 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 etrasimod compared to placebo demonstrated greater improvement from baseline in the total IBDQ score. Changes in IBDQ total score at Week 12 from baseline with etrasimod compared to placebo were 42.8 and 27.4, respectively and changes in IBDQ total score at Week 52 from baseline with etrasimod compared to placebo were 55.8 and 38.1, respectively.

ELEVATE UC 12
In ELEVATE UC 12, a total of 354 patients were randomised to receive etrasimod 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.

Of the 354 patients randomised, 89.5% and 88.8% of the patients completed Week 12 in the etrasimod and placebo group, respectively.

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, 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 etrasimod achieved clinical remission, endoscopic improvement, symptomatic remission, and mucosal healing at Week 12, compared to placebo (see Table 3).

Table 3: Proportion of patients meeting efficacy endpoints at Week 12 in ELEVATE UC 12

Endpoints	Placebo N = 112		Etrasimod 2 mg 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%	

[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
The efficacy results in patients with mMS of 4 (including ES ≥ 2 and RB subscore ≥ 1) were consistent with those of the primary analysis.

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

Early onset of symptomatic improvement
At Week 4, a greater proportion of patients treated with etrasimod compared to placebo achieved symptomatic remission (28% vs 16%) and complete symptomatic remission (12% vs 4%) defined as a SF subscore of 0 and RB subscore of 0.

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 etrasimod 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 etrasimod compared to placebo at Week 12 (10% vs 5%).

Abdominal pain and bowel urgency
At Week 12, a greater proportion of patients treated with etrasimod 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 etrasimod compared to placebo demonstrated greater improvement from baseline in the total IBDQ score. Changes in IBDQ total score at Week 12 from baseline with etrasimod compared to placebo were 47.5 and 30.2, respectively.

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. Estimated steady state etrasimod accumulation ratio ranges from about 2- to 3–fold. The pharmacokinetics of etrasimod 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 pharmaceutical 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).

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, 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 bound to human plasma proteins (97.9%), primarily albumin and mainly distributed in the plasma fraction of whole blood with blood-to-plasma ratio of 0.7.

Biotransformation

Etrasimod is extensively metabolised via CYP2C8 (38%), CYP2C9 (37%), and CYP3A4 (22%), and with minor contributions via CYP2C19 and CYP2J2. The major circulating component in plasma is unchanged etrasimod and main metabolites M3 and M6. Etrasimod contributes to the majority of S1P pharmacology (> 90%). Etrasimod is extensively metabolised by oxidation, dehydrogenation, and conjugation by UGTs and sulfotransferases.

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

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.

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

Effect of etrasimod on other medicinal products

In vitro studies indicate that, at the recommended dose of 2 mg once daily, etrasimod is unlikely to show any clinically relevant interaction potential for CYP or membrane transporters.

Pharmacokinetics in specific groups of 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 and subjects with normal renal function (see section 4.2). The severe renal impairment cohort included 2 subjects with eGFR ≤ 29 mL/min (not on haemodialysis), and 6 subjects with ESRD who received haemodialysis prior to administration of etrasimod. The impact of haemodialysis performed after etrasimod administration has not been 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 (see section 4.2). 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.

Elderly
Population pharmacokinetic analyses showed that age did not have an effect on the pharmacokinetics of etrasimod in patients over 65 years of age (n=40 (3.7%) of patients were aged ≥ 65). There is no meaningful difference in the pharmacokinetics in elderly patients compared to younger patients.

Body weight
The systemic exposure of etrasimod 2 mg is not altered by body weight differences to a clinically meaningful extent in patients with body weight ≥ 40 kg. In patients with body weight below 40 kg, an approximately 1.5-fold increase in exposure is predicted (see section 4.2).

Sex, race, and ethnicity
Population pharmacokinetics analysis showed that sex, race, or ethnicity has no clinically significant effect on etrasimod pharmacokinetics.

Paediatric
A population pharmacokinetics analysis predicted similar etrasimod exposures in adult and older adolescent (16 to < 18 years old) patients with UC.

No data are available on administration of etrasimod to paediatric or adolescent patients below the age of 16 years.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for etrasimod in humans with the following exception: changes in the left ventricular arteries (hypertrophy/hyperplasia of the tunica media) were observed in 3- and 9- month repeat-dose toxicity studies in dogs at exposures ≥ 24 times the recommended human dose (RHD) exposure based on AUC. The relevance of this finding for humans is uncertain. Furthermore, the exposure to the most abundant human metabolites (M3 and M6) was investigated in rats only. The relevance for humans is uncertain.

Fertility and reproductive toxicity

Etrasimod did not affect male and female fertility in rats up to the highest dose tested, representing an approximate 467-fold exposure margin based on human systemic exposures at the RHD for males and 21-fold for females.

Etrasimod administration to pregnant rats and rabbits daily during organogenesis resulted in post-implantation loss with a corresponding lower number of viable foetuses and foetal external, visceral, and/or skeletal malformations and variations in the absence of maternal toxicity. Malformations were observed at the lowest dose tested in rats with maternal plasma AUC approximately 5 times that in humans at the RHD. The exposure at the no-adverse-effect dose (2 mg/kg/day) in the rabbit was approximately 0.8 times, that in humans at the RHD of 2 mg/day.

Following daily oral administration of etrasimod through pregnancy and lactation in rats, decreased mean pup weights, lower pup viability, and reduced fertility and reproductive performance (reduction in implantations and increased preimplantation loss) in F1 pups were observed. 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

Tablet core

Mannitol (E421)
Microcrystalline cellulose (E460i)
Sodium starch glycolate (Type A)
Magnesium stearate (E470b)

Tablet coating

Brilliant blue FCF aluminium lake (E133)
Indigo carmine aluminium lake (E132)
Tartrazine aluminium lake (E102)
Macrogol 4000 (E1521)
Poly(vinyl alcohol) (E1203)
Talc (E553b)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store Below 25^0C. Store in the original pack, in order to protect from moisture.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle closed with a polypropylene cap, desiccant integrated directly into the cap. Pack size of 30 film-coated tablets.

Aluminium blister strip laminated to an oriented polyamine (oPA) film and integrated desiccant layer (HDPE/LDPE), with a paper/aluminium/LDPE or aluminium/LDPE backing. Pack size of 28 or 98 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Pharmaceuticals Israel Ltd
9 Shenkar St Herzliya Pituach
Israel

8. MARKETING AUTHORISATION NUMBER(S)

177-69-38002-99
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