ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Velsipity 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains etrasimod 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.

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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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]**

	Placebo N = 135		Etrasimod 2 mg N = 274		Treatment difference (95% CI)[a]
	n	%	n	%	
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%	
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%	

	Placebo N = 135		Etrasimod 2 mg N = 274		Treatment difference (95% CI)[a]
	n	%	n	%	
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%	
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.

[1] $p < 0.001$.

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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with etrasimod in one or more subsets of the paediatric population in UC (see section 4.2 for information on paediatric use).

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 clinicially 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

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

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

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package 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 an 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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1790/001
EU/1/23/1790/002
EU/1/23/1790/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 February 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Almac Pharma Services (lreland) Limited
Finnabair Industrial Estate
Dundalk, A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Portadown, Craigavon, BT63 5UA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of etrasimod in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The main objective of the programme is to increase awareness about the important identified and potential risks of the medicinal product, specifically in regard to macular oedema, symptomatic bradycardia (including conduction disorders), serious opportunistic infections, malignancy, embryofoetal toxicity, serious liver injury, and neurological events of PRES or convulsion.

The MAH shall ensure that in each Member State where etrasimod is marketed, all healthcare professionals who are expected to prescribe have access to/are provided with the following educational package:

- Healthcare Professional Checklist
- Patient/Caregiver Guide
- Pregnancy-Specific Patient Card.

Healthcare Professional Checklist
The Healthcare Professional Checklist shall contain the following key messages:

Before first dose
Lists of tests and checks to be conducted prior to treatment initiation with etrasimod:

- An electrocardiogram (ECG) should be obtained in all patients to assess for pre-existing cardiac abnormalities.
- Etrasimod should not be used in 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.
  - 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.
- Cardiologist advice should be obtained in patients with symptomatic bradycardia and other pre-existing cardiac conditions, to determine overall benefit risk and the most appropriate monitoring strategy.
- Caution should be taken when initiating etrasimod in patients taking medicines known to decrease heart rate.
- Etrasimod should not be used in patients with any active infection or live attenuated vaccine immunisations within the last 4 weeks.
- A recent complete blood count (CBC), including lymphocyte count, should be obtained.
  - Etrasimod should not be used in patients with an absolute lymphocyte counts < 0.2 x 10^9/L.
- Recent transaminase and bilirubin levels should be available.
  - Etrasimod must not be used in patients with severe hepatic impairment.
- In women of childbearing potential, a pregnancy test must be negative and patients must be counselled on risk for the foetus. Provide a pregnancy-specific patient card to all female patients of childbearing potential.
  - Etrasimod must not be used during pregnancy or in women of childbearing potential not using effective contraception.
- It is recommended that patients with history of diabetes mellitus, uveitis, and/or underlying/co-existing retinal disease, who are at increased risk of developing macular oedema, undergo an ophthalmic evaluation prior to treatment initiation.
  - Patients with macular oedema should not use etrasimod.

Monitoring activities during and after treatment
- In patients with resting heart rate < 50 bpm, second-degree AV block [Mobitz type I], or a history of myocardial infarction or heart failure, monitoring is recommended after the first dose:
  - 4-hour monitoring for signs and symptoms of symptomatic bradycardia (including dizziness), and hourly pulse and blood pressure. 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.
- Recommendation for measuring blood pressure regularly while on treatment.
- 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.
- Recommendation for assessments of CBC periodically during treatment.
- Treatment interruption if a patient develops a serious infection.
- 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.
- 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.
- The use of live attenuated vaccine should be avoided for at least 2 weeks after discontinuation of treatment with etrasimod.
- Hepatic enzymes should be monitored at months 1, 3, 6, 9, and 12 on therapy and periodically thereafter. Etrasimod should be discontinued if significant liver injury is confirmed.
- Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for at least 14 days after stopping etrasimod. Pregnancy testing should be repeated regularly. If a woman becomes pregnant during treatment, etrasimod must be immediately discontinued.
- Patients with a history of diabetes mellitus, uveitis, and/or an underlying/co-existing retinal disease should undergo an ophthalmic evaluation **regularly**. An ophthalmic evaluation should be made in patients developing a change in vision.
- In patients without risk factors for macular oedema (such as history of diabetes mellitus, uveitis, and/or retinal disease), 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 while on treatment if there is a change in vision.
- Patients should be cautioned against exposure to sunlight without protection to prevent the development of cutaneous malignancies. Patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.
- Patients should be counselled for symptoms of PRES. A complete physical and neurological examination should be done and an MRI considered for patients who develop unexpected neurological or psychiatric symptoms/signs or any symptoms suggestive of an increase of intracranial pressure, or accelerated neurological deterioration. Treatment with etrasimod should be discontinued if PRES is suspected.

Patient/Caregiver Guide

The Patient/Caregiver Guide shall contain the following key messages:

- Etrasimod should not be used in patients with myocardial infarction, unstable angina pectoris, stroke, TIA, decompensated heart failure requiring hospitalisation, or NYHA Class III/IV heart failure in the last 6 months or with a history or presence of Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker.
- Patients should have a baseline ECG prior to receiving the first dose.
- For patients with certain heart conditions, heart rate should be monitored for 4 hours after the first dose of etrasimod, for signs and symptoms of symptomatic bradycardia (including dizziness), including hourly pulse and blood pressure checks. An ECG before and after the 4 hours should also be performed for these patients.

- Patients should inform their prescriber if etrasimod treatment is interrupted for 7 or more consecutive days, since a new examination of the heart may be necessary before starting the treatment again.
- Information to report immediately: symptoms indicating low heart rate (such as dizziness, vertigo, nausea, or palpitations) when starting etrasimod. Caution should be taken with concomitant use of medicines that slow the heart rate. Patients should tell any doctor they see that they are being treated with etrasimod.
- Description of signs/symptoms of infections the patient needs to be aware of, during and after treatment, so that they can seek attention from their HCP.
- Description of signs/symptoms of serious liver injury that the patient needs to be aware of, including unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine.
- Etrasimod must not be used during pregnancy or in women of childbearing potential not using effective contraception.
    - Women of childbearing potential must use effective contraception during and for at least 14 days after discontinuation of treatment.
    - Women of childbearing potential must have a negative pregnancy test before treatment initiation with etrasimod. Patients should tell their doctors straight away if they become pregnant while taking etrasimod. Pregnancy testing should be repeated regularly.
- Description of risk factors and signs/symptoms of macular oedema and the need to seek medical attention if symptoms develop.
- Be informed to notify their doctor if suspicious skin lesions are observed and to limit their exposure to sun light and UV (ultraviolet) light, by wearing protective clothing and applying regular sunscreen (with high sun protection factor).
- Description of signs/symptoms of PRES and PML the patient needs to be aware of, including developing severe headache, feel confused, or have seizures and loss of vision.

Pregnancy-Specific Patient Card

The pregnancy-specific patient card (for women of childbearing potential) shall contain the following key messages:

- Etrasimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception due to its embryotoxic potential.
- Women of childbearing potential must have a negative pregnancy test before treatment initiation, use effective contraception during treatment and for at least 14 days after treatment discontinuation.
- Pregnancy testing should be repeated regularly.
- If a woman becomes pregnant while on treatment, etrasimod must be immediately discontinued and follow-up examinations should be performed.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Velsipity 2 mg film-coated tablets
etrasimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains tartrazine.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
28 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1790/001 (28 tablets)
EU/1/23/1790/002 (98 tablets)
EU/1/23/1790/003 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Velsipity 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Velsipity 2 mg film-coated tablets
etrasimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains tartrazine.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original container.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1790/003 (30 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Velsipity 2 mg film-coated tablets
etrasimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MAH logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Velsipity 2 mg film-coated tablets
etrasimod

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, your doctor will give you a patient card, which contains important safety information that you need to be aware of. Keep this patient card with you.

What is in this leaflet

1. What Velsipity is and what it is used for

Velsipity contains the active substance etrasimod, which belongs to a group of medicines known as sphingosine-1-phosphate receptor modulators.

Velsipity is used in adults and adolescents aged 16 years and older for the treatment of moderately to severely active ulcerative colitis (UC). Ulcerative colitis is an inflammatory disease of the large bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or cannot take these medicines, you may be given Velsipity to reduce the signs and symptoms of the disease.

The active substance in Velsipity, etrasimod, prevents lymphocytes (a type of white blood cell) from travelling from the lymph nodes (part of the body's immune system that contains lymphocytes) into the blood. These lymphocytes are involved in the inflammation that is linked to the development of ulcerative colitis. By reducing the number of lymphocytes circulating in the blood surrounding the large bowel, etrasimod helps to reduce bowel inflammation and the symptoms associated with the disease.

2. What you need to know before you take Velsipity

Do not take Velsipity
- if you are allergic to etrasimod or any of the other ingredients of this medicine (listed in section 6);
- if your healthcare professional has told you that you have a severely weakened immune system;

- if you have had a heart attack, unstable angina pectoris (chest pain caused by interruptions in the heart's blood supply that occurs at rest or without an obvious trigger), stroke, transient ischaemic attack (TIA, also known as a mini-stroke) or certain types of severe heart failure in the last 6 months;
- if you have certain types of arrhythmia (irregular or abnormal heartbeat) – your doctor will check your heart before starting treatment;
- if you have a severe active infection or active chronic infection, such as hepatitis (inflammation of the liver) or tuberculosis;
- if you have cancer;
- if you have severe liver problems;
- if you are pregnant or a woman of childbearing potential not using effective contraception.

Warnings and precautions
Talk to your doctor or, pharmacist before taking Velsipity if:
- you have a slow heart rate or you are taking or have recently taken medicines that slow your heart rate (such as beta blockers or calcium channel blockers);
- you have ever had a stroke or other diseases related to blood vessels in the brain;
- you have problems with your liver;
- you have an infection;
- you have low levels of lymphocytes (a type of white blood cell);
- you have recently had or are planning to have a vaccination;
- you have ever had problems with your vision or other symptoms of build-up of fluid in the back of the eye;
- you have inflammation of the eye;
- you have diabetes (which can cause problems with your eyes);
- you have high blood pressure;
- you have severe lung disease, such as pulmonary fibrosis (lung damage with tissue scarring and thickening), asthma or chronic obstructive pulmonary disease (a type of lung disease marked by permanent damage to lung tissues).

Slow heart rate and irregular heart rhythm
Before you start taking Velsipity, your doctor will check your heart using an electrocardiogram (ECG; a test of the heart's electrical activity). This is because Velsipity can cause a temporary decrease in heart rate and other heart rhythm disorders when starting treatment. When this happens, you may feel dizzy or tired or be consciously aware of your heartbeat, or your blood pressure may drop. If these effects are severe, tell your doctor, because you may need treatment right away. If you restart treatment again after stopping for 7 or more days in a row, your doctor may re-check your heart using an ECG.

If you have certain heart conditions, your doctor will also monitor you for at least the first 4 hours after your first dose. Your doctor will ask you to stay at the hospital or clinic for 4 hours and will measure your pulse and blood pressure every hour after taking the first dose of Velsipity. You should have an ECG performed before the first dose of Velsipity and after the 4-hour monitoring period. If after the 4-hour period you have a very slow or decreasing heart rate, or if your ECG shows abnormalities, you may need to be monitored for a longer period until these have resolved.

High blood pressure
As Velsipity can increase your blood pressure, your doctor may want to check your blood pressure regularly.

Infections
Velsipity lowers the levels of white blood cell in your blood (particularly the lymphocyte count). White blood cells fight infection. While you are taking Velsipity (and for up to about 2 weeks after you stop taking it), you may be more likely to get infections, and any infection that you already have may get worse. Talk to your doctor if you develop an infection. If you think you have an infection,

have a fever, feel like you have the flu, have shingles or have a headache accompanied by a stiff neck, with sensitivity to light, nausea, rash, and/or confusion or seizures (fits) (these may be symptoms of meningitis and/or encephalitis caused by a fungal or herpes viral infection), contact your doctor straight away, because it could be serious and life-threatening.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported with medicines similar to Velsipity. PML is a rare viral brain infection that may lead to severe disability or death. PML symptoms include disturbance of vision, progressive weakness, clumsiness, memory loss or confusion. If you develop any of these symptoms, speak to your doctor straight away. Your doctor will consider performing further tests to evaluate this condition and will stop your treatment with Velsipity if PML is confirmed.

Macular oedema
Velsipity can cause a problem with your vision called macular oedema (swelling of the macula, the central part of the retina at the back of the eye). The risk of developing macular oedema is higher if you have diabetes, uveitis (inflammation of the uvea, the layer beneath the white of the eyeball), or certain other eye problems. If you have any of these conditions, your doctor will check your vision before you start taking Velsipity and regularly during treatment. If you do not have these conditions, your doctor will check your vision within 3-4 months after starting treatment. Tell your doctor about any changes in your vision while on Velsipity.

Call your doctor straight away if you have any of the following:
- blurriness or shadows in the centre of your vision;
- a blind spot in the centre of your vision;
- sensitivity to light;
- unusually coloured (tinted) vision.

Cancer
Velsipity weakens your immune system. This increases your risk of developing cancers, in particular skin cancers. Skin cancers have been reported with medicines similar to Velsipity. Talk to your doctor straight away if you notice any skin nodules (e.g., shiny pearly nodules), patches or open sores that do not heal within weeks. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in colour, shape, or size over time. Since there is a risk for skin cancer, you should limit your exposure to sunlight and UV (ultraviolet) light by wearing protective clothing and regularly applying sunscreen (with high sun protection factor).

Posterior reversible encephalopathy syndrome (PRES)
Posterior reversible encephalopathy syndrome (PRES) is a condition where the brain swells. PRES symptoms include headache, changes in vision, reduced awareness, confusion, and seizures (fits). If you develop any of these symptoms, speak to your doctor straight away.

Vaccinations
If you need to receive a vaccine, seek your doctor’s advice first. Vaccines may not work as well as they should during your treatment with Velsipity. You are advised to make sure your vaccinations are up-to-date before you start treatment. So-called live vaccines may trigger the infection that they are supposed to prevent and should therefore be given at least 4 weeks before you start treatment, or at least 2 weeks after you stop taking Velsipity.

Liver function tests
Velsipity may affect your liver function. Tell your doctor straight away if you develop any of the following symptoms: yellowing of your skin or the whites of your eyes, abnormally dark urine (brown coloured), pain on the right side of your stomach area (abdomen), tiredness, feeling less hungry than usual or unexplained nausea and vomiting.

Before, during and after the treatment, your doctor will request blood tests to monitor your liver function.

Lung problems
Velsipity may have an effect on the lung function. Patients with severe lung problems have a higher chance of developing these side effects.

Other treatments for ulcerative colitis
Your doctor will usually advise that you stop other treatments for ulcerative colitis with the exception of corticosteroids (like cortisone), and mesalazine. Some medicines for ulcerative colitis may also be used for other conditions. Tell your doctor about all other medicines you take. When switching from the previous treatment, because of the risk of additive immunosuppressive effects, the risk of infection may be increased for some time. Do not take any other immunosuppressive products unless your doctor has told you to do so.

Women of childbearing potential
If used during pregnancy, Velsipity can harm the unborn baby. Before you start treatment with Velsipity, your doctor will explain the risk to you and ask you to do a pregnancy test in order to ensure that you are not pregnant. Your doctor will give you a patient card which explains why you should not become pregnant while taking Velsipity. It also explains what you should do to avoid becoming pregnant while you are taking Velsipity. You must use effective contraception during treatment and for at least 14 days after stopping treatment (see "Pregnancy, contraception, and breast-feeding" in section 2).

If any of these apply to you, tell your doctor or pharmacist before taking Velsipity.

Children and adolescents
Do not give this medicine to children and adolescents aged under 16 years. This is because Velsipity has not been studied in this age group.

Other medicines and Velsipity
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because Velsipity can affect the way some other medicines work. Also, some other medicines can affect the way Velsipity works.

In particular, before taking Velsipity, tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines:
- Medicines to control your heart rate and blood pressure (beta blocker medicines and calcium channel blocker medicines); use of these medicines could strengthen the effect of Velsipity on irregular heartbeat.
- Medicines to control your heart rhythm (antiarrhythmics), or heartbeat.
- Medicines that affect your immune system; use of these medicines with Velsipity could weaken the immune system.
- Vaccines; if you need to receive a vaccine, talk to your doctor. You should not take Velsipity for at least 2 weeks before a vaccination. You should not take Velsipity for at least 4 weeks after receiving a live vaccine.
- Fluconazole (an anti-fungal treatment) and certain other medicines can increase the levels of Velsipity in the blood, which increases the risk of side effects with Velsipity. It is recommended that you do not take these while also taking Velsipity and your doctor will advise you on this.
- Rifampicin, enzalutamide, and certain other medicines can decrease the levels of Velsipity in the blood, reducing its effectiveness. It is recommended that you do not take these while also taking Velsipity and your doctor will advise you on this.

Velsipity may slightly increase the levels of hormones released from some contraceptive pills. You will still be protected from pregnancy, but your chances of side effects from contraceptive pills may be higher. If you have any side effects, talk to your doctor or pharmacist.

Pregnancy, contraception, and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy and contraception
Do not use Velsipity during pregnancy, if you are trying to become pregnant, or if you are a woman who could become pregnant and you are not using effective contraception. If Velsipity is used during pregnancy, there is a risk of harm to the unborn baby. If you are a woman who could become pregnant, your doctor will inform you about this risk before you start treatment with Velsipity and will ask you to do a pregnancy test in order to ensure that you are not pregnant. You must use effective contraception while taking Velsipity and for at least 14 days after you stop taking it. Ask your doctor about reliable methods of contraception.

Your doctor will give you a patient card which explains why you should not become pregnant while taking Velsipity.

If you do become pregnant while taking Velsipity, tell your doctor straight away. Your doctor will likely stop treatment (see "If you stop taking Velsipity" in section 3) and pre-natal checks will be performed to monitor the health of the unborn baby.

Breast-feeding
You should not breast-feed while you are taking Velsipity. This is to avoid a risk of side effects for the baby since Velsipity may pass into breast milk.

Driving and using machines
Velsipity is not expected to have an influence on your ability to drive and use machines. You may, however, feel dizzy after taking Velsipity. If this happens, do not drive or use machines.

Velsipity contains tartrazine (E102)
The colouring agent in Velsipity contains tartrazine (E102), which may cause allergic reactions.

Velsipity contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Velsipity

Velsipity will be started under the supervision of a doctor who is experienced in treating ulcerative colitis. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How to take
- The recommended dose of Velsipity is one 2 mg tablet taken once daily.
- Take Velsipity with food for the first 3 days. After this, you can take Velsipity each day with or without food.
- Swallow the tablet whole with water. Do not split, crush, or chew the tablet before swallowing as it may change how much medicine gets into your body.

If you take more Velsipity than you should
If you have taken more Velsipity than you should, call your doctor straight away or go to a hospital straight away. Take the medicine pack and this package leaflet with you.

If you forget to take Velsipity
If you forget to take a dose of Velsipity, take the next dose at your usual time. Do not double the dose.

If you stop taking Velsipity
Do not stop taking Velsipity or change your dose without talking to your doctor first. If your doctor decides to pause your treatment for 7 days or more in a row, the medicine must be taken with food for the first 3 days after you restart taking Velsipity. After that you can take Velsipity with or without food.

If you restart Velsipity after stopping your treatment for 7 days or more in a row, the effect on heart rate that may be seen when treatment is first started may re-occur and you may need to be monitored at the hospital or clinic. Do not restart Velsipity after stopping it for more than 7 days without seeking advice from your doctor.

Velsipity will stay in your body for up to 14 days after you stop taking it. Your white blood cell count (lymphocyte count) may remain low for up to about 2 weeks and side effects described in this leaflet may still occur (see "Possible side effects" in section 4) during this period.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor or pharmacist immediately if you notice any of the side effects listed below, which could become serious:

Common (may affect up to 1 in 10 people)
- bradycardia (slow heart rate)
- hypertension (high blood pressure)
- urinary tract infection (infection of the parts of the body that collect and pass out urine)
- lower respiratory tract infection (infection of the lower airways or lungs)

Uncommon (may affect up to 1 in 100 people)
- atrioventricular block (a type of heart rhythm disorder)
- macular oedema (swelling in the macula, the central part of the retina at the back of the eye)

Other side effects
Tell your doctor or pharmacist immediately if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- lymphopenia (low levels of lymphocytes, a type of white blood cell)

Common (may affect up to 1 in 10 people)
- hypercholesterolaemia (high blood cholesterol levels)
- headache
- feeling dizzy
- increased liver enzyme levels in blood tests, which can be a sign of problems with your liver function
- neutropenia (low levels of neutrophils, a type of white blood cell)
- visual impairment

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Velsipity

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle, blister, and carton after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special temperature storage conditions.
- Store in the original package in order to protect from moisture.
- Do not use this medicine if you notice any damage or signs of tampering with the pack.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Velsipity contains

- The active substance is etrasimod. Each film-coated tablet contains etrasimod arginine equivalent to 2 mg etrasimod.
- The other excipients are:

  Tablet core
  Magnesium stearate (E470b), mannitol (E421), microcrystalline cellulose (E460i), sodium starch glycolate (Type A)

  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), and titanium dioxide (E171)

What Velsipity looks like and contents of the pack
Velsipity 2 mg is a green, round, film-coated tablet of approximately 6 mm diameter with “ETR” on one side and “2” on the other side.

Pack sizes:

- Bottle of 30 film-coated tablets
- Blisters of 28 film-coated tablets
- Blisters of 98 film-coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Brussels
Belgium

Manufacturers
Almac Pharma Services (lreland) Limited
Finnabair Industrial Estate
Dundalk, A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Portadown, Craigavon, BT63 5UA
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
Pfizer NV/SA
Tél/Tel: +32 (0)2 554 62 11

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel: +370 5 251 4000

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Magyarország
Pfizer Kft.
Tel.: +36 1 488 37 00

Česká republika
Pfizer, spol. s r.o.
Tel: +420 283 004 111

Malta
Vivian Corporation Ltd.
Tel: +356 21344610

Danmark
Pfizer ApS
Tlf.: +45 44 20 11 00

Nederland
Pfizer bv
Tel: +31 (0)800 63 34 636

Deutschland
PFIZER PHARMA GmbH
Tel: +49 (0)30 550055-51000

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Ελλάδα
Pfizer Ελλάς A.E.
Τηλ: +30 210 6785800

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

España
Pfizer, S.L.
Tel: +34 91 490 99 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 21 423 5500

France
Pfizer
Tél: +33 (0)1 58 07 34 40

România
Pfizer Romania S.R.L.
Tel: +40 (0) 21 207 28 00

Hrvatska
Pfizer Croatia d.o.o.
Tel: +385 1 3908 777

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0)1 52 11 400

Ireland
Pfizer Healthcare Ireland Unlimited Company
Tel: 1800 633 363 (toll free)
+44 (0)1304 616161

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
Pfizer Ελλάς A.E. (Cyprus Branch)
Τηλ: +357 22817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel: +371 670 35 775

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer AB
Tel: +46 (0)8 550 520 00

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.