swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Velsipity

International non-proprietary name: etrasimod
Pharmaceutical form: film-coated tablets
Dosage strength(s): 2 mg
Route(s) of administration: oral
Marketing authorisation holder: Pfizer AG
Marketing authorisation no.: 69377
Decision and decision date: approved on 10 September 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

5-ASA	5-aminosalicyclic acid
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CPK	Creatine phosphokinase
CRP	C-reactive protein
CYP	Cytochrome P450
DDI	Drug-drug interaction
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
ED_{50}	Median effective dose
EMA	European Medicines Agency
ERA	Environmental risk assessment
ESRD	End-stage renal disease
FDA	Food and Drug Administration (USA)
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good Laboratory Practice
hERG	Human ether-a-go-go-related gene
HPLC	High-performance liquid chromatography
HR	Heart rate
Hs-CRP	High-sensitivity C-reactive protein
hS1P	Human sphingosine 1-phosphate
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
JAK	Janus kinase
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
mMS	Modified Mayo Score
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporters
PBPK	Physiology-based pharmacokinetics

PD	Pharmacodynamics
P-gp	P-glycoprotein
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PRES	Posterior reversible encephalopathy syndrome
PSP	Pediatric study plan (US FDA)
QD	Once daily
RMP	Risk management plan
S1P	Sphingosine 1-phosphate
$S1P_{1,2,3,4,5}$	Sphingosine 1-phosphate receptors 1,2,3,4, and 5
SAE	Serious adverse event
SDEIs	Sponsor-designated events of interest
SOC	System Organ Class
SwissPAR	Swiss Public Assessment Report
$T_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to reach C_{max}
TNF	Tumour necrosis factor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UC	Ulcerative colitis
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for etrasimod in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with Singapore.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose is 2 mg etrasimod taken once daily.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 June 2023
Formal control completed	30 June 2023
List of Questions (LoQ)	27 October 2023
Response to LoQ	2 February 2024
Preliminary decision	21 March 2024
Response to preliminary decision	5 April 2024
Labelling corrections and/or other aspects	21 May 2024
Response to labelling corrections and/or other aspects	14 June 2024
2nd Labelling corrections and/or other aspects	4 July 2024
Response to 2nd labelling corrections and/or other aspects	26 July 2024
3rd Labelling corrections and/or other aspects	19 August 2024
Response to 3rd labelling corrections and/or other aspects	2 September 2024
Final decision	10 September 2024
Decision	approval

3 Medical context

Ulcerative colitis (UC) is a chronic inflammatory condition characterised by relapsing and remitting episodes of inflammation of the colon's mucosa, almost always involving the rectum. Onset is typically between 15 and 30 years of age with a second smaller peak between 50 and 70 years of age. UC is characterised by a balanced gender ratio.
Diarrhoea is the main symptom of UC. It may be associated with blood in the stool. Other symptoms include frequent bowel movements, abdominal pain, urgency, tenesmus, and incontinence. The onset of symptoms is usually gradual and may be self-limiting. The severity of symptoms ranges from mild (defined as up to 4 bowel movements per day) to severe (defined as more than 10 bowel movements per day with cramps and bleeding). Systemic symptoms may occur, such as fever, fatigue, and weight loss.
The severity of UC can be estimated using the Mayo Score. In the clinical development programme for etrasimod, a modified version of the Mayo Score (Modified MS (mMS)) consisting of the 3 sub-scores: stool frequency, rectal bleeding, and findings on endoscopy was used. It ranges from 0 to 9 points, with 0 points indicating no active disease and 9 points indicating severe disease.

The treatment goals of UC depend on the severity of symptoms. Important criteria of clinical efficacy refer to the induction of clinical remission, the maintenance of steroid-free remission, the prevention of hospitalisation and/or surgery, and improved quality of life. In most cases, mesalazine and corticosteroids represent the backbone of treatment. Novel treatment strategies include antibodies targeted against tumour necrosis factors (TNF), interleukin-12/-23, or integrin.

Etrasimod is a sphingosine 1-phosphate (S1P) receptor modulator that partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood and thereby lowering the number of activated lymphocytes in the tissue.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

5 Nonclinical aspects

5.1 Pharmacology

Etrasimod showed *in vitro* full agonism towards the human $S1P_1$ receptor (EC_{50} values 0.2 nM to 57 nM depending on assay and endpoint) and partial agonism on $S1P_4$ and $S1P_5$ receptors (EC_{50} also within nanomolar range), but no relevant activity on $S1P_2$ and $S1P_3$ receptors. The *in vitro* potency of etrasimod to elicit β-arrestin recruitment and $S1P_1$ receptor internalisation was similar to that of authorised S1P receptor modulators, whereas etrasimod was slightly less potent in terms of eliciting G protein signalling (GTPγS binding and cAMP accumulation) than the comparators. The main human plasma metabolites M3 and M6 showed *in vitro* a similar receptor selectivity but lower potency than etrasimod.
Etrasimod is also a potent agonist on $S1P_1$ receptors in mice, rats, and dogs, as demonstrated by *in vitro* assays (EC_{50} 3-9 nM) and *in vivo*. Oral administration induced a significant reduction in lymphocyte counts (IC_{50} 23-46 ng/mL and ED_{50} 0.03-0.2 mg/kg, based on PK/PD modelling). Hence, these species were suitable for nonclinical safety testing. Activity of etrasimod on other S1P receptors from animal species was not investigated.
In a mouse colitis model, oral administration of etrasimod at ≥3 mg/kg/day significantly inhibited development of the disease. The results of this study support the use of etrasimod in the proposed indication, although it should be noted that etrasimod was given prophylactically and not as therapy.
The studies on secondary pharmacodynamics indicate a low off-target interaction potential of etrasimod.
Etrasimod was adequately tested in a safety pharmacology core battery according to ICH S7A/B. Regarding the cardiovascular system, etrasimod *in vitro* induced activation of the hERG potassium current (+31% at 1 µM, which is 193-fold the clinical free plasma C_{max} of 5.2 nM). In addition, etrasimod activated the rectifying potassium channel I_{KAch} at clinically relevant concentrations. This is considered related to the pharmacological activity on $S1P_1$ receptors on myocytes and associated with a clinical outcome of transient bradycardia. In telemeterised dogs, slight effects were observed following single oral administration of 10-40 mg/kg, including transient increases in arterial pressure, decreases in heart rate, and shorter QTc interval. Bradycardia and increased blood pressure also occurred in the clinical studies with etrasimod treatment, but QT interval was not affected at the recommended dose of 2 mg.
In single-dose studies in rats with doses up to 350 mg/kg, no adverse effects on central nervous system (CNS) and respiratory function were observed up to plasma exposures that are significantly above the clinical exposure. The brain and spinal cord were highly exposed to drug-derived radioactivity in the distribution study, but no adverse effects on the CNS were noted in either the safety pharmacology study or the general toxicity studies. In the clinical studies, headache and dizziness were common side effects observed with etrasimod treatment.

5.2 Pharmacokinetics

The pharmacokinetics of etrasimod were adequately characterised in the animal species used for safety assessment. In mice, rats, and dogs, the plasma T_{max} following oral administration was generally within 2 and 8 h. Plasma $t_{1/2}$ in rodents (5-14 h) was shorter than in humans (30 h), whereas $t_{1/2}$ in dogs (22-53 h) was comparable to that in humans. In rats and dogs, etrasimod plasma exposure generally increased proportionally to dose and slight accumulation occurred upon repeated administration of 25-250 mg/kg/day to rats and 2-15 mg/kg/day to dogs.
Etrasimod was quantified in plasma from rat pups at mean pup-to-maternal concentration ratios from 23% to 73%. Milk transfer of etrasimod or metabolites was not studied but is likely. Thus, etrasimod should not be used by breastfeeding women. This is adequately addressed in the Information for healthcare professionals. Etrasimod displayed high plasma protein binding in humans (97.9%), mice and rats (99.1%), rabbits (98.2%), and dogs (99.2%). Based on *in vitro* and *in vivo* studies, etrasimod does not preferentially distribute to blood cells.

In rats, [^{14}C]etrasimod-related radioactivity showed rapid and wide tissue distribution, including tissues behind the blood-brain barrier. There was binding and retention of drug-derived radioactivity to melanin-containing tissues.
Etrasimod was extensively metabolised *in vitro* in hepatocytes from rats, dogs, monkeys, and humans. No human-specific metabolite was identified in these studies, but some minor metabolites were only detected in monkey and human incubations. The *in vitro* metabolic profiles correlated with the *in vivo* profiles in rats, dogs, and humans. Metabolites M6 and M3 were the most abundant plasma metabolites in humans and rats but only minor metabolites in dogs. Both metabolites are considered sufficiently characterised by the toxicity studies with etrasimod in rats.
[^{14}C]etrasimod-related radioactivity was primarily excreted via faeces in rats and dogs, as it was observed in the human mass balance study.

5.3 Toxicology

The toxicological profile of etrasimod was evaluated in mice, rats, rabbits (reproductive toxicity), and dogs. The selection of rat and dog for safety assessment is considered acceptable, as both species are pharmacologically relevant and sufficiently comparable to humans with regard to pharmacokinetics. The route of administration and frequency of dosing in the nonclinical studies are consistent with the proposed clinical setting (once-daily oral dosing). Etrasimod was administered to animals as a salt formulation (etrasimod L-arginine), with dose levels based on the free acid molecular weight.
The general toxicity studies included repeat-dose studies up to a treatment duration of 6 months in rats and 9 months in dogs. In addition, studies up to 3 months were conducted in mice to select doses for the carcinogenicity study. Etrasimod doses up to 150 mg/kg/day in rats, 15 mg/kg/day in dogs, and 20 mg/kg/day in mice were tolerated and considered as NOAELs. The corresponding plasma exposures were multiples of the human exposure at the 2 mg/day dose. Across species, treatment with etrasimod caused decreases in body weight/body weight gain and food consumption.
The primary target organs of etrasimod were the lymphoid system, lung, liver, and heart. In the long-term studies, effects on the target organs (see below) occurred at the lowest dose levels, which were associated with plasma exposures ≥210-fold (rat) and ≥24-fold (dog) the clinical exposure. The applicant did not consider these effects as adverse, as they were either related to the intended pharmacology, were of minimal to mild severity, not associated with clinical signs, did not compromise the health of the animals, and/or were reversible.

- *Lymphoid system:* Reductions in lymphoid cell populations in the periphery and in lymphoid tissues occurred in all species; these are related to the desired pharmacological effect. Lymphopenia was observed in the clinical studies, and the potential risks for infections and effects on vaccination by the pharmacological mode of action are addressed in the Information for healthcare professionals. In the animal studies, there was no evidence of opportunistic infections.
- *Lung:* Treatment with etrasimod induced increased lung weights in all species and alveolar changes in mice and dogs (alveolar histiocytosis, fibrosis). The histological changes in the lung were not associated with morphologic changes in hypoxia-sensitive tissues or functional consequences, although it should be noted that specific lung function tests were not conducted in the general toxicity studies. Respiratory effects were observed in the clinical studies with etrasimod and other S1P modulators; the Information for healthcare professionals contains a respective warning note.
- *Liver:* Increased liver weight, centrilobular hepatocyte hypertrophy, bile duct hyperplasia, and/or changes in clinical pathology parameters were observed in animals at doses at or below the NOAEL. In rats, hepatocellular necrosis and ALT increases occurred at high, non-tolerated doses (≥250 mg/kg/day). In the clinical studies, increases in ALT were a common finding, and serious liver injury is considered an important potential risk of etrasimod treatment.
- *Heart:* Non-reversible, etrasimod-related hypertrophy and hyperplasia of the tunica media in the left ventricular arteries of the heart were observed in the dog studies with treatment duration ≥3 months. There were no correlating findings of myocardial degeneration or necrosis, congestive heart failure, or effects on ECG parameters in these studies. The relevance of this finding for

clinical use is uncertain; the available clinical data for etrasimod did not indicate a risk of cardiovascular effects with longer treatment duration. Similar histological changes in the dog heart were also reported for the S1P modulator ponesimod (Ponvory®)[1,2].

In the chronic toxicity studies, lower prostate gland weights without histological correlate were observed in rats at ≥150 mg/kg/day and in dogs at all dose levels (≥2 mg/kg/day). These findings were considered secondary to the lower body weight. In addition, etrasimod treatment of dogs led to increased ocular discharge and associated conjunctivitis, but no such observation was made in the clinical studies.

Etrasimod tested negative for genotoxic potential *in vitro* and *in vivo* according to ICH S2(R1).
Etrasimod was not carcinogenic in rats up to the highest dose level (20 mg/kg/day), corresponding to 80-fold (males) and 179-fold (females) the clinical exposure. Mineralisation in the brain was observed as a non-neoplastic effect of etrasimod at all dose levels. A similar finding was also reported for the S1P modulator ponesimod (Ponvory®) and considered to be rat-specific and not clinically relevant[2]. In mice, an increased incidence of vascular tumours (haemangioma and haemangiosarcoma) was observed at ≥6 mg/kg/day. Plasma exposure at the NOEL for carcinogenicity in mice (2 mg/kg/day) was 19-fold the clinical exposure. Vascular tumours in mice have also been described following treatment with other S1P receptor modulators and are considered a species-specific effect.
Etrasimod did not affect spermatogenesis and fertility in male and female rats up to doses that were associated with plasma exposures 467-fold (males, 200 mg/kg/day) and 21-fold (females, 4 mg/kg/day) the clinical exposure. In studies on embryofetal development in rats and rabbits, administration of etrasimod led to embryofetal toxicity and teratogenic effects at all dose levels in rats (≥1 mg/kg/day) and in rabbits at ≥10 mg/kg/day. Plasma exposure at the developmental NOAEL in rabbits (2 mg/kg/day) was below the clinical exposure. In the pre- and postnatal development study in rats, decreased pup weights were seen at all dose levels (≥0.4 mg/kg/day), pup mortality was increased at ≥2 mg/kg/day, and parturition was affected at the high dose of 4 mg/kg/day. Postweaning assessment showed persistently lower body weights in F1 males and reduced fertility (increased pre-implantation loss) in F1 females from maternal animals treated with 4 mg/kg/day. The etrasimod-related effects on embryofetal development are consistent with those observed with other S1P receptor modulators and considered related to the function of $S1P_1$ receptors in embryogenesis. The risks are adequately reflected in the Information for healthcare professionals.
Etrasimod tested negative for phototoxic potential in the *in vitro* 3T3 Neutral Red Uptake test.
Impurities are controlled according to ICH Q3A/B and ICH M7. There are no concerns with regard to the excipients.
Based on the ERA, the therapeutic use of etrasimod is not expected to pose a risk to the environment.

5.4 Nonclinical conclusions

In conclusion, a comprehensive study package covering pharmacology, pharmacokinetics, and toxicology has been submitted for etrasimod. The effects observed in the nonclinical safety studies are consistent with those observed with other S1P receptor modulators. The relevant nonclinical data are mentioned in the Information for healthcare professionals. From the nonclinical point of view, the application is approvable.

[1] U.S. Food and Drug Administration, Center for Drug Evaluation and Research: Application number 213498Orig1s000 (Ponvory, ponesimod), Non-clinical review(s); 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213498Orig1s000PharmR.pdf.
[2] Swissmedic, Swiss Public Assessment Report Ponvory, dated 21 January 2022. Available from: https://www.swissmedic.ch/dam/swissmedic/de/dokumente/zulassung/swisspar/68114-ponvory-01-swisspar-20220121.pdf.download.pdf/SwissPAR_Ponvory.pdf

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption and biopharmaceutical development
Etrasimod was characterised as a BCS II compound (low solubility, high permeability).

Administration of the commercial 2 mg tablet with a high-fat, high-calorie meal had no impact on etrasimod C_{max} or AUC. The median tmax was prolonged from 4 hours to 6 hours after fed administration. The data support administration of etrasimod independently of food.

Dose proportionality
There was a dose-proportional increase in etrasimod exposures after administration of single doses within the range of 0.1 mg to 5 mg. After administration of multiple doses between 0.7 mg and 2 mg, there was a slightly more than dose-proportional increase in etrasimod exposures. Evaluations by dose level indicated a dose-proportional increase in etrasimod exposures between 1 mg and 2 mg QD and a slightly more than dose-proportional increase between 2 mg and 3 mg once daily (QD).

Pharmacokinetics after multiple dosing
After 2 mg QD, there was a 2.3- to 2.7- fold accumulation of etrasimod C_{max} and AUC. The linearity index was close to 1, indicating time-independent pharmacokinetics. Steady state was reached within 5 to 7 days of QD dosing.

Distribution
The *in vitro* plasma protein binding of etrasimod was 97.9%. Etrasimod is bound mainly to albumin (0.0792% unbound) and α1-acid glycoprotein (1.1 -1.5% unbound) and to a lesser extent to lipoproteins (14 – 17.4% unbound). There was no overall concentration dependence of etrasimod plasma protein binding at therapeutic exposures.

The mean etrasimod *in vitro* blood-to-plasma ratio ranged from 0.643 to 0.821, indicating low distribution to blood cells. This showed good correlation with the data obtained after administration of a ^{14}C-labelled dose, where the blood-to-plasma ratio of radioactivity was 0.662 for C_{max} and 0.612 for AUC_{inf}.

Metabolism & elimination
In vitro data
Etrasimod was metabolised by CYP2C8 (38%), 2C9 (37%) and 3A4 (22%), and to a lesser extent by CYP2C19 and 2J2. Furthermore, several UGTs are involved in the *in vitro* metabolism of etrasimod.

Clinical data
After administration of a single ^{14}C-labelled dose, unchanged etrasimod was the most abundant compound in plasma, accounting for 49.3% of total plasma radioactivity, followed by the oxidative metabolites M3 (AR503641) and M6 (AR504344), each accounting for approximately 8% of total plasma radioactivity. The remaining plasma radioactivity was due to several minor metabolites, each accounting for less than 5% of total plasma radioactivity.

Both M3 and M6 are pharmacologically active, but their *in vitro* activity was lower than the activity of etrasimod (M3 10- to 91-fold less potent at $S1P_1$ and $S1P_5$, M6 3- to 1.5-fold less potent at $S1P_1$ and $S1P_5$. Considering a mean metabolite/parent ratio (based on AUC_{inf}) of 28.3% for M3 and of 25.4% for M6, the metabolites' contribution to the total pharmacological activity is low.

After administration of a single ^{14}C-labelled dose, 4.89% and 82.0% of the radioactive dose was excreted in urine and faeces, respectively.

The most abundant compounds excreted in faeces were M3 (AR503641) and M36 (APD334-oxy sulfate), accounting for 22.1% and 18.9% of the radioactive dose, respectively. Unchanged etrasimod accounted for 11.2% of the radioactive dose.

No unchanged etrasimod was detected in urine. It was possible to ascribe the small amount of radioactivity excreted in urine to several minor metabolites, each accounting for less than 1% of the total radioactivity.

The half-life of etrasimod is 35 to 40 h. The half-life of M3 and M6 is approximately 55 h.

Special populations

After administration of a single 2 mg dose of etrasimod to subjects with mild, moderate, or severe hepatic impairment, etrasimod C_{max} was not affected by hepatic impairment, but its AUC increased with decreasing hepatic function up to 1.57-fold in subjects with severe hepatic impairment. M3 C_{max} and AUC increased with decreasing hepatic function. The increases were higher than for etrasimod (up to 3-fold for AUC_{inf} in severe hepatic impairment). M6 C_{max} and AUC were higher in subjects with hepatic impairment compared to healthy controls, but there was no consistent trend of increasing metabolite exposures with decreasing hepatic function. The increases were higher than for etrasimod (up to 2-fold for AUC_{inf} in severe impairment).

The impact of severe renal impairment on the pharmacokinetics of etrasimod and its 2 main metabolites was limited, supporting the recommendation that no dose adjustment for renal impairment of any degree is required.

The impact of additional covariates including, but not limited to age, body weight, sex, hepatic and renal function, patient status, and others on etrasimod exposures were investigated in a pop PK analysis.

The dataset included 1,079 subjects, of whom 61.9% were UC patients and 38.1% healthy subjects. The majority (72.8%) of the subjects were white. Hepatic function based on the Child-Pugh classification was missing for the UC patients, i.e. for 61.9% of the subjects in the dataset. Hepatic function was assumed to be normal in all healthy subjects (36.1%). The subjects with mild (n=8), moderate (n=8), or severe hepatic impairment (n=6) came from the dedicated hepatic impairment study. The majority of the subjects (70.3%) had normal renal function. The dataset included 25.3%, 1.3%, 0.2%, 0.3%, and 0.6% of subjects with mild, mild to moderate, moderate, severe renal impairment, or end-stage renal disease (ESRD), respectively, i.e. there were only very few subjects with impaired renal function in the dataset.

The overall body weight and age range in the dataset was 41.4 to 138 kg and 16 to 78 years, respectively. The majority (96.2%) of the subjects were ≥18 to <65 years old, 3.5% were ≥65 to <75 years old, 2 (0.2%) subjects were ≥75 years old, and only 1 (0.1%) subject was <18 years old.

The final etrasimod pop PK model was a 2-compartment model with combined zero-order/first-order absorption and first-order elimination. The final model included the following main covariate relationships:

- Effect of body weight on apparent clearance and apparent intercompartmental clearance (AUC,ss ↓ with weight ↑)
- Effect of age on apparent clearance (AUC,ss ↑ with age ↑)
- Effect of female sex on apparent clearance (AUC,ss ↑)
- Effect of healthy subject on apparent clearance (AUC,ss ↓)
- Effect of bilirubin on apparent clearance (AUC,ss ↑ with bili ↑)

- Effect of estimated glomerular filtration rate on apparent clearance (AUC,ss ↑ with GFR ↓)
- Effect of tobacco use on apparent clearance (AUC,ss ↓)
- Effect of body weight on apparent central and peripheral volume (AUC,ss ↓ with weight ↑)

The changes in etrasimod exposures due to the covariates were small, i.e. mostly within 80 to 125% of the reference.

The final model described the data reasonably well.

Interactions

IMPACT OF OTHER DRUGS ON ETRASIMOD

In vitro data

Etrasimod was metabolised by CYP2C8 (38%), 2C9 (37%), and 3A4 (22%), and to a lesser extent by CYP2C19 and 2J2. Etrasimod was not a substrate for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2.

Clinical data

Clinical interaction studies were conducted with fluconazole (moderate inhibitor of CYP2C9 and CYP3A4 and strong inhibitor of CYP2C19), gemfibrozil (strong inhibitor of CYP2C8), rifampin (moderate inducer of CYP2C9, CYP2C8, CYP3A4, and CYP2C19) and itraconazole (strong inhibitor of CYP34).

Based on the results of these studies, which are summarised in the Information for healthcare professionals, the following recommendations apply:

- Co-administration of etrasimod with moderate or strong inhibitors of at least 2 of the 3 main CYPs involved in its metabolism (2C8, 2C9, and 3A4) should be avoided.
- Co-administration of etrasimod with moderate or strong inhibitors of CYP2C8 and/or CYP3A4 is not recommended in CYP2C9 poor metabolisers.
- Co-administration of etrasimod with moderate or strong inducers of at least 2 of the 3 main CYPs involved in its metabolism (2C8, 2C9, and 3A4) is not recommended.

IMPACT OF ETRASIMOD ON OTHER DRUGS

Based on the *in vitro* data, the interaction potential of etrasimod with CYPs or transporters as a perpetrator appeared to be low. The only clinical interaction study conducted with etrasimod as a perpetrator was an oral contraceptive interaction study with pharmacokinetic and pharmacodynamic endpoints, where no clinically relevant changes were observed.

Pharmacodynamics

SECONDARY PHARMACOLOGY (SAFETY)

Bradycardia
Etrasimod caused dose/concentration-dependent bradycardia, which was most pronounced within the first 8 hours post-dose. The effect of dose titration on bradycardia was negligible in healthy subjects.

Additional investigations of daily or hourly titration schedules confirmed the limited impact of titration on the occurrence and severity of bradycardia. The mean nadir change from time-matched baseline

of heart rate (HR) (Day 1, primary endpoint) was similar for all treatments. Titration appeared to postpone, but not attenuate, bradycardia.

The risk of arrhythmias was also similar for the different regimens with or without titration.

The relationship between etrasimod plasma concentrations and heart rate (HR) was further investigated in a PKPD analysis. The PKPD model accounted for the circadian changes of HR, supine or non-supine position during ECG recordings, and the development of tolerance during etrasimod treatment. The final PKPD model described the HR data reasonably well.

Simulations with the final PKPD model confirmed that titration postponed etrasimod-induced bradycardia from Day 1 to Day 6, but did not abolish or attenuate it.

In summary, the data support the recommendation of not titrating the etrasimod dose, but rather to monitor certain patients after the first dose.

QTc interval
The impact of etrasimod on QTc was investigated after multiple ascending doses of 2 mg, 3 mg, and 4 mg QD (2 mg QD for 7 days, 3 mg QD for 5 days, 4 mg QD for 2 days). A single dose of 400 mg moxifloxacin served as active control.

The mean etrasimod C_{max} on Day 14 (last day on 4 mg) was 1.9-fold higher than on Day 7 (last day on 2 mg). Compared to the simulated C_{max} in UC patients after therapeutic dosing, it was 1.6-fold higher.

Because of the transient bradycardia caused by etrasimod, several methods of QT correction were evaluated. The best correction was obtained with QTcF and the individual correction factor QTcS.

The tQT study was formally “negative”, as the upper limit of the 90% CI in the by-time-point analysis never exceeded the critical threshold of 10 ms. However, for both QTcF and QTcS, it was >9 ms on several occasions, most frequently after 4 mg QD.

There were no absolute QTc values >480 ms and no QTc prolongation >30 ms under etrasimod.

Moxifloxacin showed the expected effect on QTc, i.e. assay sensitivity was demonstrated.

In summary, after 2 mg QD, clinically relevant QTc prolongation appears unlikely, but it cannot be excluded after higher exposures.

6.2 Dose finding and dose recommendation

The **dose-finding study APD334-003** was a Phase 2, randomised, double-blind, placebo-controlled study in subjects with moderately to severely active UC. Patients were randomly assigned in a 1:1:1 ratio to etrasimod 1 mg, etrasimod 2 mg, or placebo once daily for 12 weeks. Etrasimod 2 mg demonstrated a statistically significant greater reduction in the mMS compared to placebo, whereas etrasimod 1 mg did not. The safety profile was similar for both doses. Therefore, selection of the higher 2 mg dose for the Phase 3 studies can be adopted.

6.3 Efficacy

Two pivotal Phase 3 studies were submitted for this application. Both were randomised, double-blind, and placebo-controlled studies, with a 2:1 randomisation to etrasimod 2 mg or placebo.

Both pivotal studies included identical 12-week double-blind induction treatment periods. Treatment in study **APD334-302** ended after the 12-week double-blind induction treatment period. Study **APD334-301** had a treat-through design that included an additional 40-week double-blind treatment period after the 12-week induction for a total treatment duration of 52 weeks (etrasimod 2 mg or placebo).

Both studies included subjects 16 to 80 years of age with UC with a mMS of 4-9 and with a history of inadequate response, loss of response, or intolerance to at least 1 conventional therapy (i.e. oral 5-aminosalicyclic acid (5-ASA), corticosteroids, thiopurines), biologic therapy, or Janus kinase (JAK) inhibitor therapy.
The inclusion criterion in both pivotal studies of mMS 4-9 is not in line with the requested indication of moderate to severe UC, as mMS 4 corresponds to mild disease. However, as the subgroup of patients with mMS 5-9 was chosen for the primary analysis population, this can therefore be accepted with the requested disease severity in the indication.

The primary endpoint was the percentage of patients achieving clinical remission at Week 12 and Week 52. This was defined as a stool frequency subscore = 0 (or = 1 with a ≥1-point decrease from baseline), a rectal bleeding subscore = 0, and an endoscopic subscore ≤1.

Overall, the treatment groups were well-balanced and represented most of the intended target-population well. In both studies, ~30% of patients had prior biologic or JAK inhibitor therapy. Overall, this is somewhat lower compared to what would be expected for the Swiss UC populations. This may be due to the high percentage of patients recruited in Eastern Europe, where the use of biologics/JAKs is rarer.
There were just 3 adolescents included in both pivotal studies and only 45 patients over 65 years of age (27 (6.2%) in study 301 and 18 (5.1%) in study 302). With only 3 adolescents, of whom only 1 received etrasimod, no firm conclusions regarding efficacy or safety in this population can be drawn.

In **study APD334-301**, all primary and secondary endpoints were met. At Week 12, 27.0% of patients in the etrasimod group achieved clinical remission, compared to only 7.4% in the placebo group. At Week 52, 32.1% of patients achieved clinical remission, compared to only 6.7% in the placebo group. The proportion of patients in corticosteroid-free remission was 32.1% (6.7% for placebo).

In **study APD334-302**, all primary and secondary endpoints were met. Treatment with etrasimod led to clinical remission in 24.8% of the patients (placebo: 15.2%).
However, the magnitude of benefit in study 302 was somewhat lower compared to study 301, due to a higher placebo response rate in this study. This may be due to certain differences in baseline values (e.g. hs-CRP). A higher percentage of patients with a lower baseline hs-CRP was observed in the placebo group in study APD334-302 compared to the 2 etrasimod groups and the other placebo group in studies APD334-301 and APD334-302. However, both placebo response rates are within the historical placebo response rates of other UC trials.

The treat-through study design has the potential for a high rate of drop-outs, especially with a placebo control group. This because the rate of patients who discontinue study treatment due to lack of efficacy or disease worsening is expected to be higher in the placebo group if the active treatment works. These drop-outs will accumulate during the whole study duration, possibly leading to a higher drop-out rate in the placebo group than the active treatment group. This was also reflected in study APD334-301 with clearly fewer patients completing the study in the placebo group (31.9%) compared to the etrasimod 2 mg group (55.7%). To a certain extent, this may support the efficacy of the active treatment compared to placebo. Nevertheless, evaluation of the overall time-course of response is somewhat hampered by the high rates of discontinuations and makes conclusions on the long-term benefits rather difficult.

Most of the **subgroup analyses** showed quite consistent results. However, after Week 12, there was no efficacy in patients over 65 years of age in either study, though efficacy could be demonstrated

after Week 52 in patients over 65 years of age. Overall, despite the limited number of participants over 65 years of age, efficacy in this subgroup was similar compared to participants below 65 years of age. Therefore, although the data in this age group are limited, this is not considered prohibitive.
Three other subgroups showed reduced efficacy after Week 12 in both studies and after Week 52, namely patients with pancolitis and patients with prior treatment failure of an anti-TNFα antibody, and patients who had received more than 1 prior biologic/JAK inhibitor. This latter subgroup even showed numerically lower response to etrasimod compared to placebo in study APD334-302. However, attenuated efficacy in patients heavily pre-treated with biologics/JAK inhibitors can be expected in these subgroups and is in line with observations from other development programmes of approved treatments for UC. In addition, the small sample sizes in the subgroup analyses do not support a firm conclusion regarding reduced efficacy.

The **open-label extension study APD334-005** included subjects with UC who completed study APD334-003 (responders and non-responders). All subjects received open-label 2 mg etrasimod orally once daily for 34 weeks according to the initial study protocol. However, a protocol amendment introduced a placebo group and, consequently, blinding; this was then reversed with a subsequent amendment that reimplemented the original study design. These changes make it difficult to allow any overall conclusion for this study. However, the study can be viewed as supporting, to a certain extent, sustained efficacy of etrasimod. In addition, a benefit of switching to 2 mg etrasimod from placebo or from the lower dose of 1 mg was seen. Overall, the efficacy of etrasimod was maintained without further increase.

6.4 Safety

The integrated safety assessment included different safety pools. The most important was the placebo-controlled UC pool (including studies APD334-003, APD334-301, and APD334-302), with 577 subjects receiving at least 1 dose of etrasimod 2 mg and 314 subjects receiving at least 1 dose of placebo, equivalent to 276.7 and 115.1 subject-years of exposure, respectively.

In the placebo-controlled UC pool, a higher percentage of patients had TEAEs in the etrasimod 2 mg group compared to the placebo group (60% vs 51.6%, respectively). However, the proportion of patients with any Grade 3 or higher TEAE or any SAE was relatively low with etrasimod 2 mg (5.4% and 4.5%, respectively) and lower than with placebo (6.1% and 5.4%, respectively).
The most common TEAEs (occurring in ≥1% of subjects) in the etrasimod 2 mg group, which were more frequent (by ≥1% difference) in the etrasimod 2 mg group compared to placebo, were: headache, pyrexia, nausea, dizziness, gamma-glutamyltransferase increased, hypertension, urinary tract infection, ALT increased, vomiting, blood creatine phosphokinase (CPK) increased, diarrhoea, flatulence, hypercholesterolaemia, and bradycardia.

Overall, the percentage of patients with SAEs was fairly similar between the etrasimod 2 mg and placebo groups (4.5% vs 5.4%) in the placebo-controlled UC pool. Most of the SAEs were single cases. One case of herpes meningitis was possibly related to etrasimod (12 days after first dose), which was also in line with an overall higher risk of infections due to the mode of action of etrasimod.

Only 1 death was reported in the whole etrasimod clinical development programme, which was due to a poorly differentiated neuroendocrine tumour. It is deemed unlikely that this would be related to the study treatment.

Sponsor-designated events of interest (SDEIs) were chosen by the applicant, based on the mechanism of action of etrasimod, prior experience with other agents acting via a similar mechanism, and disease-specific clinical judgment.
The risk of bradycardia and AV conduction delay is known with other S1P modulators and is reflected in the Information for healthcare professionals. Most events occurred on the first day of treatment. As

dose titration does not attenuate this risk, patients with pre-existing heart disease should be monitored after the first dose.
Although the percentage of patients with AEs in the nervous system was higher in the etrasimod 2 mg group compared to placebo (12.1% vs 7.3%), no pattern could be observed. There was no posterior reversible encephalopathy syndrome (PRES) in any of the studies with etrasimod; however, as this is known with other SP1 modulators, a respective warning note was included in the Information for healthcare professionals.
Across the whole clinical development programme of etrasimod in all indications, the percentage of patients with TEAEs in the neoplasms System Organ Class (SOC) was higher in the etrasimod 2 mg groups compared to placebo (10 patients 0.9% vs 2 patients 0.5%). However, only 2 of these 10 patients had malignant neoplasms. These were 1 neuroendocrine tumour (fatal case) and 1 squamous cell carcinoma of the skin. Based on the available data from a fairly small sample size and with no longer-term data available, no firm conclusions can be drawn regarding neoplasms. However, it is stated in the Information for healthcare professionals that ‘cases of malignancies (including skin malignancies) have been reported in patients treated with S1P receptor modulators’ and etrasimod is contraindicated in patients with active malignancies. This is considered to adequately reflect current knowledge.

In common with the efficacy data, safety data in patients >65 years of age are sparse. However, no prohibitive safety concerns were found in this age group.

6.5 Final clinical benefit-risk assessment

The submitted data demonstrate a statistically significant and clinically relevant benefit of etrasimod compared to placebo in the induction and maintenance treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, no response, or intolerance to conventional therapy or a biologic treatment. In both pivotal studies, the primary and key secondary endpoints were all met.

Etrasimod showed an acceptable safety profile in the submitted studies and no prohibitive safety signals were detected. The proportion of subjects with SAEs was low and without any observed clusters. There was only 1 death in the whole etrasimod development programme and it is not considered related to etrasimod. S1P modulators are known for their risk of bradycardia and AV conduction delay. As dose titration does not attenuate this risk for etrasimod, patients with pre-existing heart disease should be monitored after the first dose.

Overall, taking into consideration the demonstrated clinical benefit, the safety profile, and the safety measures, the benefit-risk assessment of etrasimod is positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Velsipity was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Velsipity®

Composition

Active substances

Etrasimod (as Etrasimod-l-arginine).

Excipients

Tablet core: magnesium stearate (E 470b), mannitol (E 421), microcrystalline cellulose (E 460i), carboxymethyl starch sodium A (corresp. 0.11-0.17 mg sodium per film-coated tablet).

Tablet coating: brilliant blue FCF aluminum lake (E 133), indigo carmine aluminum lake (E 132), tartrazine aluminum lake (E 102), macrogol 4000 JP/PEG 3350, polyvinyl alcohol (partially hydrolysed) (E 1203), talc (E 553b), titanium dioxide (E 171).

Pharmaceutical form and active substance quantity per unit

2 mg film-coated tablet: Green, round, film-coated tablet of approximately 6 mm diameter, debossed with «ETR» on one side and «2» on the other side.

Indications/Uses

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

Dosage/Administration

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

Usual dosage

The recommended dose is 2 mg etrasimod taken once daily.

Special dosage instructions

Patients with hepatic disorders

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 «Contraindications» and «Pharmacokinetics»).

Patients with renal disorders

No dose adjustment is needed for patients with renal impairment (see «Pharmacokinetics»).

Elderly patients

There are limited data available on patients over 65 years and older. No clinically significant differences in the pharmacokinetics of etrasimod were observed based on age (see «Pharmacokinetics»). No dose adjustment is needed in patients over 65 years of age.
In general, use of etrasimod in patients over 65 years should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and an increased risk of adverse reactions in this population.

Children and adolescents

The safety and efficacy of etrasimod in children and adolescents have not yet been established. No data are available.

Mode of administration

Oral use.

Etrasimod should be swallowed whole and can be administered with or without food (see «Pharmacokinetics»).

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section «Composition - Excipients».
- Immunodeficient state (see «Warnings and precautions»).

- 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.
- Severe hepatic impairment.
- Active malignancies.
- During pregnancy and breast-feeding, as well as in women of childbearing potential not using effective contraception (see «Warnings and precautions» and «Pregnancy, lactation»).

Warnings and precautions

Bradyarrhythmia and atrioventricular conduction delays

Prior to treatment initiation with etrasimod, an electrocardiogram (ECG) in all patients should be obtained to assess for pre-existing cardiac abnormalities. In patients with certain pre-existing conditions, first dose monitoring is recommended (see below).

Initiation of etrasimod may result in a transient decrease in heart rate and AV conduction delays (see «Undesirable effects» and «Pharmacodynamics»).

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

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

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 «Interactions») 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 heart rate before initiation of etrasimod (see also section below and «Interactions»).

If interruption is deemed necessary, treatment with a beta-blocker can be reinitiated depending on the time of reaching the baseline heart rate.

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, first dose, 4 hour monitoring for signs and symptoms of symptomatic bradycardia 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 «Contraindications»).
Patients should be monitored with hourly pulse and blood pressure measurement during this 4 hour period. An ECG prior to and at the end of this 4 hour period is recommended.

Additional monitoring after 4 hours is recommended in patients, if at 4 hours:

- 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.

Cardiologist advice should be obtained before initiation of etrasimod in the following patients to determine overall benefit risk and the most appropriate monitoring strategy

- In patients with significant QT prolongation (QTcF ≥ 450 msec in males, ≥ 470 msec in females).
- In patients with arrhythmias requiring treatment with Class Ia or Class III anti-arrhythmic drugs.
- In patients with ischaemic heart disease, history of cardiac arrest, cerebrovascular disease, or uncontrolled hypertension.
- In patients with history of symptomatic bradycardia, recurrent cardiogenic syncope, or severe untreated sleep apnoea.

Infections

Risk of infections

Etrasimod causes a mean reduction in peripheral blood lymphocyte count to approximately 45% of baseline values at Week 52 because of reversible sequestration of lymphocytes in lymphoid tissues (see «Pharmacodynamics»). Etrasimod may, therefore, increase the susceptibility to infections (see «Undesirable effects»).
Before initiating treatment, obtain a recent complete blood count (CBC), including lymphocyte count (i.e., within the last 6 months or after discontinuation of prior UC therapy).
Assessments of CBC are also recommended periodically during treatment. Absolute lymphocyte counts < 0.2 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.

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

Patients should be instructed to report promptly 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, treatment interruption with etrasimod should be considered. Because 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 «Pharmacodynamics»).

Progressive multifocal leukoencephalopathy (PML)
PML is an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised, and that may lead to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.
No cases of PML have been reported in etrasimod-treated patients in the development programme; however, PML has been reported in multiple sclerosis patients treated with other sphingosine 1-phosphate (S1P) receptor modulators and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). Physicians should be vigilant for clinical symptoms or unexplained neurologic findings that may be suggestive of PML. If PML is suspected, treatment with etrasimod should be suspended until PML has been excluded by an appropriate diagnostic evaluation.
If PML is confirmed, treatment with etrasimod should be discontinued.
Cases of immune reconstitution syndrome (IRIS) have been reported in patients treated with S1P receptor modulators who discontinued therapy due to PML. IRIS is expressed as a possible rapid clinical deterioration of the patient’s condition. It can lead to severe neurological complications or death and is often accompanied by characteristic changes in the MRI. In patients with PML, IRIS usually occurs a few months after stopping the S1P receptor modulator. Patients should therefore be monitored for the development of IRIS for a prolonged period after discontinuation of the S1P receptor modulator and treated if necessary.

Prior and concomitant treatment with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies
In ELEVATE UC 52 and ELEVATE UC 12, patients who received etrasimod were not to receive concomitant treatment with anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies used for the treatment of UC. In ELEVATE UC 52 and ELEVATE UC

12, concomitant use of corticosteroids was allowed and did not appear to influence the safety or efficacy of etrasimod (see «Pharmacodynamics»).
Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution because of the risk of additive immune system effects during such therapy (see «Interactions»).
When switching to etrasimod from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immune system effects.

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, administer at least 4 weeks prior to initiation of etrasimod. Avoid the use of live attenuated vaccines during and for 2 weeks after treatment with etrasimod.
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 «Undesirable effects»). Recent (i.e., within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with etrasimod.
Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have hepatic enzymes checked and etrasimod should be discontinued if significant liver injury is confirmed (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 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 «Undesirable effects»). 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 «Pregnancy, lactation» and «Preclinical data»). Due to the risk to the foetus, etrasimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception (see «Contraindications» and «Pregnancy, lactation»). Before initiation of treatment, women of childbearing potential must be informed to 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 «Pregnancy, lactation»).

Macular oedema

S1P receptor modulators, including etrasimod, have been associated with an increased risk of macular oedema. An ophthalmic evaluation of the fundus, including the macula, is recommended in all patients at any time if there is any change in vision while taking etrasimod.

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

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. As there is a potential risk of skin malignancies, patients treated with etrasimod should be warned of unprotected exposure to sunlight. These patients should not receive simultaneous phototherapy with UV-B radiation or PUVA photochemotherapy.

Posterior reversible encephalopathy syndrome (PRES)

Rare cases of PRES have been reported in patients receiving other S1P receptor modulators. Such events have not been reported for etrasimod-treated patients in the development programme. 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.

Interactions with other medicinal products, CYP2C9 polymorphism
Etrasimod should not be given with any active substance or combination of substances that are moderate to strong inhibitors of two or more of the following CYP enzymes (CYP2C8, CYP2C9 and CYP3A4), as there is a risk of increased exposure to etrasimod (see «Interactions»).
The use of etrasimod is not recommended when it is 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), as there is a risk of decreased exposure to etrasimod (see «Interactions»).
The use of etrasimod is not recommended in patients known or suspected to be slow CYP2C9 metabolisers (< 5% of the population) and who are taking medicines that are moderate or potent inhibitors of CYP2C8 and/or CYP3A4, due to a risk of increased exposure to etrasimod (see «Interactions»).

Respiratory effects
Reductions in absolute forced expiratory volume over 1 second (FEV_1) and forced vital capacity (FVC) were observed in patients treated with S1P receptor modulators, including etrasimod (see «Pharmacodynamics»). Etrasimod should be used with caution in patients with severe respiratory disease (e.g., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease).

Excipients

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is almost «sodium-free».

Tartrazine

This medicinal product contains tartrazine (E 102) which may cause allergic reactions.

Interactions

Effect of Velsipity 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 drug-drug interaction potential for CYP or membrane transporters.

Effect of other medicinal products on Velsipity

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

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

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%.

The strong CYP2C8 inhibitor gemfibrozil and the strong CYP3A4 inhibitor itraconazole increased exposure (AUC) of etrasimod by 36% and 32%, respectively.

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) increases the exposure of etrasimod and is not recommended.

The use of etrasimod is not recommended in patients who are known or suspected poor metabolisers (PM) of CYP2C9 and who are taking moderate or strong inhibitors of CYP2C8 and/or CYP3A4 due to the risk of increased exposure to etrasimod.

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 CYPs (CYP2C8, CYP2C9, and CYP3A4) (e.g., rifampicin) decreases the exposure of etrasimod and is not recommended.

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

The initiation of a beta blocker with stable treatment of 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 «Warnings and precautions»).

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 «Warnings and precautions»).
Because of 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 «Warnings and precautions»).

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 «Warnings and precautions»).

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 2 weeks after discontinuation of treatment with etrasimod (see «Warnings and precautions»).

Paediatric population

Interaction studies have only been performed in adults.

Oral contraceptives

No clinically significant differences in the pharmacokinetics and pharmacodynamics of an oral contraceptive containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel were observed when

co-administered with etrasimod. Concomitant administration with etrasimod increased the AUC of ethinylestradiol and levonorgestrel by approximately 24% and 32%, respectively.

Pregnancy, lactation

Women of childbearing potential/Contraception in females

Velsipity is contraindicated in women of childbearing potential not using effective contraception (see «Contraindications»). 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 the drug 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 14 days after treatment discontinuation (see «Warnings and precautions»).
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 are limited amount of data from the use of etrasimod in pregnant women. Studies in animals have shown reproductive toxicity (see «Preclinical data»). Clinical experience with another S1P receptor modulator indicates a 2-fold higher risk of serious congenital malformations when the drug is administered during pregnancy compared to the frequency observed in the general population. Based on human experience, etrasimod may cause congenital malformations when used during the first trimester of pregnancy. Limited human data on etrasimod suggest an increased risk of abnormal pregnancy outcome. Consequently, Velsipity is contraindicated during pregnancy (see «Contraindications»).
Etrasimod should be stopped at least 14 days before a pregnancy is planned (see «Warnings and precautions»). 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.

Lactation

It is unknown whether etrasimod is excreted in human milk. A study in lactating rats has indicated excretion of etrasimod in milk (see «Preclinical data»). A risk to newborns/infants cannot be excluded. Etrasimod must not be used during breastfeeding (see «Contraindications»)

Fertility

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

Effects on ability to drive and use machines

Etrasimod has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness has been reported (see «Undesirable effects»).

Undesirable effects

Summary of the safety profile

The most common adverse drug 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 for all adverse reactions. 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, <1/10), «uncommon» (≥1/1'000, <1/100), «rare» (≥1/10'000, <1/ 1'000) and «very rare» (<1/10'000).

Table 1: Summary of adverse reactions

System Organ Class (SOC)	Very Common	Common	Uncommon
Infections and infestations		urinary tract infection[a]	
Blood and lymphatic system disorders	lymphopenia (11%)[b]	neutropenia	
Metabolism and nutrition disorders		hypercholesterolaemia[c]	
Nervous system disorders		headache, dizziness	
Eye disorders		visual impairment	macular oedema
Cardiac disorders		bradycardia[d]	atrioventricular block[e]
Vascular disorders		hypertension	
Hepatobiliary disorders		Hepatic enzyme increased	

[a] Urinary tract infection includes urinary tract infection and cystitis.

[b] Lymphopenia includes lymphopenia, lymphocyte count decreased, and lymphocyte percentage decreased.

[c] Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased.

[d] Bradycardia includes bradycardia and sinus bradycardia.

[e] Atrioventricular block includes first- or second-degree Mobitz type I

Description of specific adverse reactions and additional information

Bradyarrhythmia

In ELEVATE UC 52, bradycardia was reported on the day of treatment initiation in 1.0% of patients treated with etrasimod compared to none in patients who received placebo. On Day 2, bradycardia was reported in 1 patient (0.3%) treated with etrasimod compared to none in patients who received placebo. In ELEVATE UC 12, bradycardia was reported on the day of treatment initiation in 2.1% of patients treated with etrasimod compared to none in patients who received placebo. On Day 2, bradycardia was reported in 1 patient (0.4%) treated with etrasimod compared to none in patients who received placebo.

At initiation of etrasimod 2 mg, events of first- or second-degree Mobitz type I AV blocks were observed in 0.7% of etrasimod-treated patients compared to none in placebo in ELEVATE UC 52 and in 0.4% of etrasimod-treated patients compared to none in placebo in ELEVATE UC 12; however, in ELEVATE UC 52 and ELEVATE UC 12, Mobitz type II second- or third-degree AV blocks were not reported in patients treated with etrasimod.

Infections

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

Blood lymphocyte count reduction

The proportion of patients treated with etrasimod who experienced lymphocyte counts less than 0.2 x 109/L was 5.6% in ELEVATE UC 52 and 0.9% in ELEVATE UC 12. These events did not lead to treatment discontinuation.

Elevated hepatic enzymes

In ELEVATE UC 52, elevations of ALT to 5-fold the ULN or greater occurred in 0.7% of patients treated with etrasimod and 0.7% of patients who received placebo, and in ELEVATE UC 12 elevations occurred in 0.8% of patients treated with etrasimod and no patients who received placebo.

In ELEVATE UC 52, elevations of ALT to 3-fold the ULN or greater occurred in 4.5% of patients treated with etrasimod and 0.7% of patients who received placebo, and in ELEVATE UC 12 elevations occurred in 2.5% of patients treated with etrasimod and no patients who received placebo. 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, and 0.4% in patients who received placebo.

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 compared to < 1.5 mm Hg and < 1 mm Hg in patients receiving placebo, respectively. The increase was first detected after 2 weeks of treatment and remained within the specified average range in blood pressure increases throughout treatment. Hypertension was reported as an adverse reaction in 2.1% of patients treated with etrasimod and in 1.0% of patients who received placebo. The majority of the events were mild to moderate in severity.

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

Herpes viral infections
Cases of localised herpes viral infection were seen with S1P receptor modulators, including etrasimod. In ELEVATE UC 52, herpes zoster was reported in 0.7% of patients treated with etrasimod and in none of the patients who received placebo. In ELEVATE UC 12, herpes zoster was reported in none of the patients treated with etrasimod and in 1.7% of patients who received placebo. One case of herpes simplex meningitis was reported in a patient treated with etrasimod in an open label study.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In patients with overdosage of etrasimod, monitor for signs and symptoms of bradycardia, which may include overnight monitoring. Regular measurements of heart rate, blood pressure, and ECGs should

be performed. There is no specific antidote to etrasimod available. The decrease in heart rate induced by etrasimod can be reversed by parenteral atropine.

Properties/Effects

ATC code

L04AE05

Mechanism of action

Etrasimod is a sphingosine 1-phosphate receptor modulator that binds with high affinity to S1P receptors 1, 4 and 5 (S1P1,4,5). Etrasimod has no relevant activity on S1P2 or S1P3. Etrasimod partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood thereby lowering the number of activated lymphocytes in the tissue.
The mechanism by which etrasimod exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into sites of inflammation. The etrasimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response. Etrasimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance.

Pharmacodynamics

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

Effect on QT interval
In a thorough QT study, daily administration of etrasimod doses 2 mg (recommended dose) to 4 mg (two times recommended dose) were evaluated in healthy subjects. The mean etrasimod C_{max} was approximately 1.4- to 1.6-fold higher when 4 mg was administered than when 2 mg was administered. Under these conditions, etrasimod did not prolong QTc interval to any clinically relevant extent.

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

Peripheral blood B cells [CD19+] and T cells [CD3+], T-helper [CD3+CD4+], and T-cytotoxic [CD3+CD8+] cell subsets were all reduced, while natural killer cells and monocytes were not. T-helper cells were more sensitive to the effects of etrasimod than T-cytotoxic cells.
Peripheral blood absolute lymphocyte counts returned to the normal range in 90% of patients within 1 to 2 weeks of stopping therapy based on a population pharmacokinetic/pharmacodynamic model.

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

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

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

Clinical efficacy and safety

The efficacy of 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). Patients with prior treatment with ≥3 biologic agents or ≥2 biologics plus a JAK inhibitor approved for treatment of UC were excluded from participation in both pivotal studies.
Enrolled patients had UC confirmed by endoscopy and histopathology with the extent of disease being ≥ 10 cm from the anal verge. Patients with isolated proctitis were also included in the study provided they met all other inclusion criteria.
Disease severity was assessed on the modified Mayo score (mMS), a 3-component Mayo score (0 to 9) which consists of the following subscores (0 to 3 for each subscore): stool frequency (SF), rectal bleeding (RB), and findings on centrally read endoscopy score (ES). An ES of 2 was defined by

marked erythaema, lack of vascular pattern, any friability, and/or erosions, and a score of 3 was defined by spontaneous bleeding and ulceration. Enrolled patients had a mMS of 4 to 9 with an ES ≥ 2 and RB subscore ≥ 1.

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

ELEVATE UC 52

ELEVATE UC 52 was a treat-through study, with a total of 433 patients randomised to receive 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, with 5.5% of patients having mMS of 4, 66.5% having mMS 5 to 7 (moderately active disease), and 28% having mMS > 7 (severely active disease). 8% of enrolled patients presented with isolated proctitis. A total of 30% of patients had prior exposure to biologic/JAK inhibitors; a total of 14% of patients had exposure to > 1 biologic/JAK inhibitor and 11% of patients had prior exposure to anti-integrins. At baseline, 77% of patients were receiving oral aminosalicylates and 31% of patients were receiving oral corticosteroids.

The co primary endpoints were the proportion of patients achieving clinical remission at Week 12 and at Week 52, with clinical remission defined as SF subscore of 0 (or 1 with a ≥ 1-point decrease from baseline), RB subscore of 0, and ES ≤ 1 (excluding friability). The secondary endpoints included the proportion of patients achieving endoscopic improvement, symptomatic remission, mucosal healing, clinical response, corticosteroid-free clinical remission, and sustained clinical remission. The primary analysis was conducted at Week 12 and at Week 52 in patients with moderately to severely active disease, defined as mMS 5 to 9 (see Table 2).

A significantly greater proportion of patients treated with 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%)[i]**

	Placebo N = 135		*Etrasimod 2 mg N = 274*		*Treatment Difference (95% CI)[a]*
	n	*%*	*n*	*%*	
No prior biologic/ JAK inhibitor exposure	9/93	10%	60/194	31%	
Prior biologic/ JAK inhibitor exposure	1/42	2%	14/80	18%	
Endoscopic Improvement[c]	**19**	**14%**	**96**	**35%**	**21% (13%, 29%)[i]**
No prior biologic/ JAK inhibitor exposure	17/93	18%	76/194	39%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	20/80	25%	
Symptomatic Remission[d]	**29**	**22%**	**126**	**46%**	**25% (15%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	22/93	24%	101/194	52%	
Prior biologic/ JAK inhibitor exposure	7/42	17%	25/80	31%	
Mucosal Healing[e]	**6**	**4%**	**58**	**21%**	**17% (11%, 23%)[i]**
No prior biologic/ JAK inhibitor exposure	6/93	7%	47/194	24%	
Prior biologic/ JAK inhibitor exposure	0/42	0%	11/80	14%	
Clinical Response[f]	**46**	**34%**	**171**	**62%**	**28% (19%, 38%)[i]**
No prior biologic/ JAK inhibitor exposure	35/93	38%	132/194	68%	
Prior biologic/ JAK inhibitor exposure	11/42	26%	39/80	49%	
Week 52 Endpoints					
Clinical Remission[b]	**9**	**7%**	**88**	**32%**	**25% (18%, 32%)[i]**
No prior biologic/ JAK inhibitor exposure	7/93	8%	71/194	37%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	17/80	21%	
Endoscopic Improvement[c]	**14**	**10%**	**102**	**37%**	**27% (19%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	12/93	13%	78/194	40%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	24/80	30%	
Symptomatic Remission[d]	**25**	**19%**	**119**	**43%**	**25% (16%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	19/93	20%	97/194	50%	

	Placebo N = 135		*Etrasimod 2 mg N = 274*		*Treatment Difference (95% CI)[a]*
	n	*%*	*n*	*%*	
Prior biologic/ JAK inhibitor exposure	6/42	14%	22/80	28%	
Mucosal Healing[e]	**11**	**8%**	**73**	**27%**	**18% (11%, 25%)[i]**
No prior biologic/ JAK inhibitor exposure	10/93	11%	55/194	28%	
Prior biologic/ JAK inhibitor exposure	1/42	2%	18/80	23%	
Clinical Response[f]	**31**	**23%**	**132**	**48%**	**25% (16%, 34%)[i]**
No prior biologic/ JAK inhibitor exposure	25/93	27%	103/194	53%	
Prior biologic/ JAK inhibitor exposure	6/42	14%	29/80	36%	
Corticosteroid-free Clinical Remission[g]	**9**	**7%**	**88**	**32%**	**25% (18%, 32%)[i]**
No prior biologic/ JAK inhibitor exposure	7/93	8%	71/194	37%	
Prior biologic/ JAK inhibitor exposure	2/42	5%	17/80	21%	
Sustained Clinical Remission[h]	**3**	**2%**	**49**	**18%**	**16% (11%, 21%)[i]**
No prior biologic/ JAK inhibitor exposure	2/93	2%	41/194	21%	
Prior biologic/ JAK inhibitor exposure	1/42	2%	8/80	10%	

CI = confidence interval.

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

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

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

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

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

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

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

[h] Sustained clinical remission was defined as clinical remission at both Week 12 and Week 52.

[i] $p < 0.001$.

Supplementary analysis of mMS 4 to 9

Efficacy results in patients with mMS 4 to 9 (including ES ≥ 2 and RB subscore ≥ 1) were consistent with those in 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%).

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

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

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

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

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

Endoscopic and histologic assessment
Normalisation of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. A greater proportion of patients treated with 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%).
When defined as ES ≤ 1 and Geboes ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue), a greater proportion of patients treated with etrasimod compared to placebo achieved histologic-endoscopic mucosal improvement at Week 12 (31% vs 10%) and Week 52 (40% vs 11%).

Abdominal pain and bowel urgency
At Week 12, a greater proportion of patients treated with 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 and all 4 domain scores of the IBDQ (bowel symptoms, systemic function, emotional function, and social function) at Week 12 and at Week 52.

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

CI = confidence interval.

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

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

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

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

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

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

[g] $p < 0.05$.

[h] $p < 0.001$.

Supplementary analysis of mMS 4 to 9

Efficacy results in patients with mMS 4 to 9 (including ES ≥ 2 and RBSubscore ≥ 1) were consistent with those in 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%).

Symptomatic remission by Week 4

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

Complete symptomatic remission

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

Stool frequency and rectal bleeding subscores

Decreases in SF and RB subscores were observed as early as Week 2 in patients treated with etrasimod compared to placebo.

Cessation of rectal bleeding

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

Endoscopic and histologic assessment

Normalisation of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. A greater proportion of patients treated with 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%).

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

Abdominal pain and bowel urgency

At Week 12, a greater proportion of patients treated with 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 and all 4 domain scores of the IBDQ (bowel symptoms, systemic function, emotional function, and social function) at Week 12.

Pharmacokinetics

Following etrasimod single oral dosing, C_{max} and AUC increased approximately dose-proportionally in the dose-range studied (0.1 mg to 5 mg). Following multiple dosing, mean C_{max} and AUC increased slightly more than dose proportional from 0.7 mg to 2 mg. Steady state plasma concentrations are reached within 7 days following 2 mg once daily dosing, with a mean C_{max} of 113 ng/mL and AUC_{tau} of 2163 h*ng/mL. Steady state etrasimod accumulation is approximately 2- to 3-fold greater than single dose. The pharmacokinetics of 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 dosage forms of etrasimod is approximately 4 hours (range 2 – 8 hours). Etrasimod absorption is extensive, based on high permeability and observation of relatively little intact etrasimod eliminated in the faeces (11.2% of administered radioactive dose). Steady state exposure was reached within 7 days of dose initiation of etrasimod.

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

Distribution

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

Metabolism

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

Elimination

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

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.

Kinetics in specific patient groups

Hepatic impairment

Etrasimod is contraindicated in patients with severe hepatic impairment. No dose adjustments are needed in patients with mild or moderate hepatic impairment. The total etrasimod AUC parameters are 13%, 29%, and 57% higher in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with subjects with normal liver function for the 2 mg single dose studied.

Renal impairment

No dose adjustments are needed in patients with renal impairment as C_{max} and AUC were comparable between subjects with severe renal impairment (comprised of subjects with eGFR ≤ 29 mL/min) and subjects with normal renal function. The effect of haemodialysis on the pharmacokinetics of etrasimod was not evaluated.

Elderly patients

Population pharmacokinetic analyses showed that age did not have an effect on the pharmacokinetics of etrasimod in patients over 65 years of age. There is no meaningful difference in the pharmacokinetics in elderly patients compared to younger patients. The proportion of 65-year-old or older patients included in the analyzes was 3.7% of the total population.

Children and adolescents

A population pharmacokinetics model predicted pharmacokinetic metrics in adult and older adolescent (16 to < 18 years old) patients with UC showed negligible differences.
No data are available on administration of etrasimod to paediatric or adolescent patients below the age of 18 years.

Body weight
Systemic exposure following administration of 2 mg etrasimod does not show clinically relevant changes in patients weighing ≥ 40 kg. In patients weighing less than 40 kg, approximately 1.5-fold increase in etrasimod exposure is expected.

Gender

Sex has no clinically significant influence on etrasimod pharmacokinetics.

Race

No clinically relevant pharmacokinetic differences were observed between Japanese, Chinese, and Caucasian subjects.

Preclinical data

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

Genotoxicity

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

Carcinogenicity

Oral carcinogenicity studies of etrasimod were conducted in mice and rats. In mice administered etrasimod (0, 2, 6, or 20 mg/kg/day) for up to 104 weeks, there was an increase in haemangiosarcoma and haemangioma at 6 and 20 mg/kg/day in males and females. Systemic exposure at the No-observed-effect level (NOEL) of 2 mg/kg/day was approximately 19 times that in humans at the recommended human dose (RHD). In rats, oral administration of etrasimod (0, 2, 6, or

20 mg/kg/day) for up to 91 weeks, did not result in an increase in tumours. Plasma etrasimod exposure (AUC) at the highest dose tested in male and female rats is approximately 80 to 179 times (respectively) that in humans at the RHD.

Reproductive toxicity

Etrasimod did not adversely affect male or female fertility in rats. Plasma etrasimod exposure (AUC) at the highest dose tested was approximately 467 (males, 200 mg/kg/day) and 21 (females, 4 mg/kg/day) times systemic exposition in humans at the RHD.
Daily administration of etrasimod to pregnant rats and rabbits during organogenesis led to post-implantation loss with a correspondingly smaller number of viable fetuses and fetal external, visceral and/or skeletal abnormalities and variations without causing maternal toxicity. In rat fetuses, malformations were observed at the lowest dose tested (1 mg/kg/day), i.e. there was no dose without adverse effects (NOAEL). In rabbits, maternal plasma exposure (AUC) at NOAEL (2 mg/kg/day) was below human exposure at RHD of 2 mg/day.
Oral administration of etrasimod (0, 0.4, 2, or 4 mg/kg/day) to female rats throughout pregnancy and lactation resulted in decreased mean pup weights at all dose levels during the preweaning period, lower pup viability at 2 and 4 mg/kg/day, and reduced fertility and reproductive performance (reduction in implantations and increased preimplantation loss) in F1 pups at the highest dose tested. 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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Special precautions for storage

Store in the original package in order to protect from moisture.
Do not store above 30°C.
Keep out of the reach of children.

Authorisation number

69377 (Swissmedic).

Packs

Blister-packs of 28 (2 x 14) film-coated tablets. [B]

Marketing authorisation holder

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