

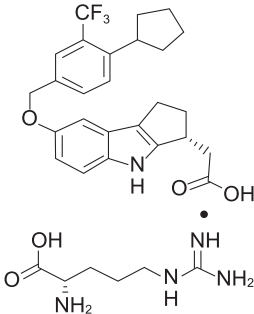
Simod™

(E t r a s i m o d)

Film-coated Tablets 2mg

DESCRIPTION

Simod (Etrasimod) contains a sphingosine 1-phosphate (S1P) receptor modulator, supplied as Etrasimod arginine. The chemical name of Etrasimod arginine is L-Arginine, (3R)-7-[[4-cyclopentyl-3-(trifluoromethyl)phenyl]methoxy]-1,2,3,4-tetrahydrocyclopent[b]indole-3-acetate (1:1). Its molecular formula is C₃₂H₄₀F₃N₅O₅ and the structural formula is:



Etrasimod Arginine

QUALITATIVE & QUANTITATIVE COMPOSITION:

Simod (Etrasimod) Tablets available for oral administration as:

Simod Tablets 2mg
Each film-coated tablet contains:
Etrasimod Arginine equivalent to Etrasimod... 2mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Etrasimod is a sphingosine-1-phosphate (S1P) receptor modulator that binds to S1P receptors 1, 4 and 5 (S1P1,4,5) and is a balanced G-protein and beta-arrestin agonist at S1P1. Etrasimod has minimal activity on S1P3 and no activity on S1P2. Etrasimod partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood thereby lowering the number of activated lymphocytes in the tissue.

The mechanism by which Etrasimod exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into sites of inflammation. The Etrasimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response known to be involved in driving UC pathology. Etrasimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance.

Pharmacokinetics

Absorption

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

Effect of food

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 (V_z/F) of 66L. Etrasimod is highly bound to human plasma proteins (97.9%), primarily albumin and mainly distributed in the plasma fraction of whole blood with blood-to-plasma ratio of 0.7.

Metabolism

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

Elimination

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

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

Special Population

Patients with Renal Impairment

No dose adjustments are needed in patients with renal impairment as C_{max} and AUC were comparable between subjects with severe renal impairment and subjects with normal renal function.

Patients with 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 2mg single dose studied.

Pediatric

A population pharmacokinetics analysis predicted similar Etrasimod exposures in adult and older adolescent (16 to < 18 years old) patients with Ulcerative Colitis. No data are available on administration of Etrasimod to pediatric or adolescent patients below the age of 16 years.

THERAPEUTIC INDICATIONS

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

DOSAGE AND ADMINISTRATION

Assessments, Medications, and Vaccinations Prior to First Dose of Simod (Etrasimod)

Before initiation of treatment with Simod (Etrasimod), assess the following:

Pre-Dosing Assessments

Medical Criterion	Assessment Actions
Cardiac Evaluation	Obtain an electrocardiogram (ECG) to determine whether pre-existing conduction abnormalities are present. In patients with certain pre-existing conditions, advice from a cardiologist should be sought.
Complete Blood Count	Obtain a recent CBC including lymphocyte count (i.e., within the last 6 months or after discontinuation of prior UC therapy).
Liver Function Tests	Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels.
Ophthalmic Assessment	In patients with a history of diabetes mellitus, uveitis, retinal disease, uncontrolled hypertension or older patients, obtain an evaluation of the fundus, including the macula prior to initiation of Simod (Etrasimod).
Vaccinations	Update immunizations in agreement with current immunization guidelines prior to initiating Simod (Etrasimod) therapy. If live attenuated vaccine immunizations are required, administer at least 4 weeks prior to initiation of Etrasimod.
Pregnancy	Pregnancy must be excluded before start of treatment as Simod (Etrasimod) may cause fetal harm. Counsel the patient about the risk of becoming pregnant while taking Simod (Etrasimod).
Skin Examination	Obtain a skin examination prior to or shortly after initiation of Simod (Etrasimod). If a suspicious skin lesion is observed, it should be promptly evaluated
Current or Prior Medications	Determine if patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction. If patients are taking anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with Simod (Etrasimod).
Recommended Dosage	The recommended dose is 2mg Simod (Etrasimod) taken once daily orally.

Missed dose

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

Dose interruption

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

Special Population

Elderly

No dose adjustment is needed in patients over 65 years of age. Simod (Etrasimod) should be used with caution in elderly patients over 65 years of age, given the limited data available and potential for an increased risk of adverse reactions in this population.

Patient with Renal Impairment

No dose adjustment is needed for patients with renal impairment.

Patient with Hepatic Impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. Simod (Etrasimod) should not be used in patients with severe hepatic impairment.

Pediatric

The safety and efficacy of Simod (Etrasimod) in children and adolescents less than 16 years of age have not yet been established. Given the limited data in adolescents aged 16 and over, Simod (Etrasimod) should be used with caution especially when body weight is less than 40kg due to the potential for increase in exposure.

Important Administration Points

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

Tablets should be swallowed whole with water and not be split, crushed or chewed.

CONTRAINDICATIONS

Etrasimod is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipient of product.
- with immunodeficient state.
- who in the last 6 months experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or New York Heart Association (NYHA) Class III/IV heart failure.
- 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.
- with severe active infections, active chronic infections such as hepatitis or tuberculosis.
- with active malignancies.
- with severe hepatic impairment.

- during pregnancy and in women of childbearing potential not using effective contraception.

ADVERSE REACTIONS

Very common
Lymphopenia.

Common

Urinary tract infection, lower respiratory tract infection, neutropenia, hypercholesterolemia, headache, dizziness, visual impairment, bradycardia, hypertension and hepatic enzyme increased.

Uncommon

Macular oedema and atrioventricular block.

“To report SUSPECTED ADVERSE REACTIONS to Getz Pharma’s Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363.”

PRECAUTIONS

Infections

Etrasimod may increase the risk of infections. Obtain a complete blood count (CBC) before initiation of treatment. Monitor for infection during treatment and for 5 weeks after discontinuation. Consider interruption of treatment if a serious infection develops. Avoid use of live attenuated vaccines during and for up to 5 weeks after treatment.

Bradyarrhythmia and Atrioventricular Conduction Delays

Etrasimod may result in a transient decrease in heart rate and AV conduction delays. Obtain an electrocardiogram (ECG) to assess for preexisting cardiac conduction abnormalities before starting treatment. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate.

Women of Childbearing Potential

Etrasimod may cause fetal harm. Due to the risk to the fetus, Etrasimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed about this risk to the fetus, must have a negative pregnancy test, and must use effective contraception during treatment and for at least 14 days after treatment discontinuation.

Macular Oedema

Etrasimod has been associated with an increased risk of macular edema. Obtain a baseline evaluation of the fundus, including the macula, near the start of treatment with Etrasimod. Periodically conduct an evaluation of the fundus, including the macula, while on therapy and any time there is a change in vision. Macular edema over an extended period of time (i.e., 6 months) can lead to permanent visual loss. Consider discontinuing Etrasimod if macular edema develops.

Liver Injury

Elevations of aminotransferases may occur in patients receiving Etrasimod. Obtain transaminase and bilirubin levels, if not recently available (i.e., within last 6 months), before initiation of Etrasimod. Obtain transaminases and bilirubin in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Discontinue Etrasimod if significant liver injury is confirmed.

Increased Blood Pressure

Monitor blood pressure during treatment with Etrasimod and manage appropriately.

Malignancies

Cases of malignancies (including cutaneous malignancies) have been reported in patients treated with S1P receptor modulators. If a suspicious skin lesion is observed, it should be promptly evaluated. Since there is a potential risk of malignant skin growths, patients treated with Etrasimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA photochemotherapy.

Posterior Reversible Encephalopathy Syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving S1P receptor modulators. If a patient develops any neurological or psychiatric symptoms/signs (e.g., cognitive deficits, behavioral changes, cortical visual disturbances, or any other neurological cortical symptoms/signs), any symptom/sign suggestive of an increase of intracranial pressure, or accelerated neurological deterioration, the physician should promptly schedule a complete physical and neurological examination and should consider an MRI. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, discontinue treatment with Etrasimod.

Respiratory Effects

Reductions in absolute forced expiratory volume over 1 second (FEV1) and forced vital capacity (FVC) were observed in patients treated with S1P receptor modulators, including Etrasimod. Etrasimod should be used with caution in patients with severe respiratory disease (e.g., pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease).

Unintended Additive Immune System Effects from Prior Treatment with Immunosuppressive or Immune-Modulating Drugs

When switching to Etrasimod from drugs with prolonged immune effects, consider the half-life and mode of action of these drugs to avoid unintended additive immunosuppressive effects.

Immune System Effects After Stopping Etrasimod

After stopping Etrasimod, lymphocyte counts returned to the normal range in 90% of subjects within 4 to 5 weeks of stopping Etrasimod. Use of immunosuppressants within this period may lead to an additive effect on the immune system, and therefore monitor patients receiving concomitant immunosuppressants for infectious complications up to 5 weeks after the last dose of Etrasimod.

Interaction with other Medicinal Products, CYP2C9 Polymorphism

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

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

The use of Etrasimod is not recommended in patients who are known or suspected to be CYP2C9 poor metabolizers (< 5% of the population) and who take medicinal products that

are moderate or strong inhibitors of CYP2C8 and/or CYP3A4 due to the risk of increased exposure of Etrasimod.

Effects on Ability to Drive and Use Machines

Etrasimod has no or negligible influence on patient's ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness has been reported.

Pregnancy

Etrasimod should be stopped at least 14 days before a pregnancy is planned. 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 fetus associated with treatment and follow up examinations should be performed. Based on human experience Etrasimod may cause congenital malformations when administered during the first trimester of pregnancy.

Nursing Mothers

It is unknown whether Etrasimod is excreted in human milk. A risk to newborns/infants cannot be excluded. Etrasimod should not be used during breast-feeding.

DRUG INTERACTIONS

Anti-Arhythmic Drugs and QT Prolonging Drugs

A transient decrease in heart rate and AV conduction delays may occur when initiating Etrasimod. Because of the potential additive effect on heart rate, Etrasimod may increase the risk of QT prolongation and Torsade's de Pointes with concomitant use of Class Ia and Class III anti-arrhythmic drugs and QT prolonging drugs. Seek the advice of a cardiologist before initiating Etrasimod treatment with Class Ia (e.g., quinidine, procainamide), Class III anti-arrhythmic drugs (e.g., amiodarone, sotalol), or other drugs that prolong the QT interval.

Beta-Blockers or Calcium Channel Blockers

A transient decrease in heart rate and AV conduction delays may occur when initiating Etrasimod. Concomitant use of Etrasimod in patients receiving stable beta blocker treatment did not result in additive effects on heart rate reduction. However, the risk of additive heart rate reduction following initiation of beta blocker therapy with stable Etrasimod treatment or concomitant use with other drugs that may decrease heart rate is unknown. Etrasimod can be initiated in patients receiving stable doses of beta blocker treatment. Seek the advice of a cardiologist before initiating a beta blocker in a patient receiving stable Etrasimod treatment or concomitant use with other drugs that may decrease heart rate (e.g., calcium channel blockers).

Anti-Neoplastic, Immune-Modulating, or Non-Corticosteroid Immunosuppressive Therapies

Avoid concomitant administration of Anti-Neoplastic, Immune-Modulating, or Non-Corticosteroid Immunosuppressive Therapies during and in the weeks following administration of Etrasimod. When switching from drugs with prolonged immune effects, consider the half-life and mode of action of these drugs to avoid unintended additive immunosuppressive effects.

Moderate to Strong Inhibitors of CYP2C9 and CYP3A4

Increased exposure of Etrasimod was observed with concomitant use with a drug that is a moderate inhibitor of CYP2C9 and a moderate inhibitor of CYP3A4 (i.e., fluconazole). Concomitant use with a drug that is a moderate to strong inhibitor of CYP2C9 and a moderate to strong inhibitor of CYP3A4 is not recommended.

CYP2C9 Poor Metabolizers Using Moderate to Strong Inhibitors of CYP2C8 or CYP3A4

Increased exposure of Etrasimod in patients who are CYP2C9 poor metabolizers is expected with concomitant use of moderate to strong inhibitors of CYP2C8 or CYP3A4. Concomitant use is not recommended.

Rifampin

Concomitant use with a drug that is a combined CYP3A4 (strong), CYP2C8 (moderate) and CYP2C9 (moderate) inducer (i.e., rifampin) decreases exposure to Etrasimod. Concomitant use is not recommended.

Vaccination

Vaccinations may be less effective if administered during and for up to 2 weeks after discontinuation of Etrasimod treatment. The use of live attenuated vaccine may carry the risk of infection and should therefore be avoided during Etrasimod treatment and for at least 2 weeks after discontinuation of Etrasimod treatment.

OVERDOSAGE

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

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Simod (Etrasimod) Tablets 2mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

**Please read the contents carefully before use.
This package insert is continually updated from time to time.**

Manufactured by:



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