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Etrasimod: A Next-Generation S1P Receptor Modulator for Ulcerative Colitis — Mechanistic Insights and Clinical Progress

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Abstract Etrasimod, a next-generation oral selective sphingosine-1-phosphate (S1P) receptor modulator, has emerged as a promising treatment for immune-mediated inflammatory diseases (IMIDs), most notably moderate-to-severe ulcerative colitis (UC). Acting primarily on S1PR1, S1PR4, and S1PR5, etrasimod effectively reduces gastrointestinal inflammation by retaining lymphocytes in lymphoid tissues, thereby minimising systemic immunosuppression and associated risks. Etrasimod provides better safety, a favorable pharmacokinetic profile, and a short washout period when compared to first-generation modulators, improving patient adherence and efficacy. Its therapeutic potential has been highlighted by clinical trials, such as the ELEVATE UC 12 and ELEVATE UC 52 studies, which showed notable improvements in clinical remission and mucosal healing when compared to placebo. With a tolerable safety profile and convenience of once-daily oral dosing, etrasimod stands out as an important advancement in the management of UC and holds further potential in other IMIDs, representing a step forward in targeted, patient-friendly immune modulation.

Keywords Etrasimod; Sphingosine-1-phosphate receptor modulator; Ulcerative colitis; Immune-mediated inflammatory diseases; Targeted immunomodulation; Pharmacokinetics; Safety profile

1. Introduction

A broad spectrum of chronic diseases referred to as Immune-mediated inflammatory diseases (IMIDs) cause tissue injury and sustained inflammation as a result of dysregulated or aberrant immune responses. These include inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), as well as systemic conditions like psoriasis, multiple sclerosis, and atopic dermatitis. IMIDs share similar underlying mechanisms despite differences in clinical manifestations and the organs involved: When environmental stimuli cause a genetically predisposed immune system to react improperly, chronic inflammation and unsuccessful tissue repair result[1].

In inflammatory bowel disease (IBD), especially in

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ulcerative colitis (UC), activated immune cells, mainly CD4+ T lymphocytes, invade the intestinal mucosa. As these T cells develop into pro-inflammatory subtypes like Th1 and Th17, they produce cytokines like interleukin-17 (IL-17), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α). Chemokines like CCL20 worsen inflammation by increasing the number of effector T cells and antigen-presenting cells in the gastrointestinal tract. The mucosa is harmed, ulcers develop, and the classic symptoms of UC—bloody diarrhoea, stomach discomfort, and an overwhelming need to void—are brought on by this continuous immunological reaction[2].

IMIDs remain to pose a significant therapeutic challenge regardless of advances in diagnosis and treatment. Traditional treatments such as corticosteroids, immunomodulators, and aminosalicylates often show limited efficacy, carry adverse effects, and lose effectiveness over time. Although biologic agents against TNF, integrins, or interleukin pathways have revolutionised the treatment of the disease, they have detriments such as high expense, risks for immunogenicity, parenteral administration requirements, and differential results over the long term. There continues to be a substantial need for novel therapies with enhanced safety, simplicity of administration, and long-term activity because there is a considerable percentage of non-responders or a subsequent relapse[3].

The sphingosine-1-phosphate (S1P) signalling pathway is a therapeutic area that is receiving more interest. A lipid mediator with bioactive qualities, S1P helps immune cells survive by controlling lymphocyte migration, preserving vascular integrity, and more. Five subtypes of G-protein-coupled receptors (S1PR1–5), each with unique roles in immune control, influence their actions. S1PR1 is very important for lymphocyte release into the bloodstream from lymph nodes. By preventing lymphocyte migration to inflammatory sites, pharmacological regulation of S1PR1 prevents local immunological activation while permitting systemic immune monitoring[4].

This strategy is embodied by Etrasimod, a next-generation oral selective modulator of S1PR1, S1PR4, and S1PR5. Etrasimod reduces gastrointestinal inflammation effectively without drastically compromising the immune system by keeping lymphocytes in lymphoid tissues. In contrast to first-generation modulators like fingolimod, etrasimod has better safety, a more desirable pharmacokinetic profile, a reduced half-life, and more predictable washout. These characteristics make it an alternative for several IMIDs in addition to UC. The rationale for exploring etrasimod in UC lies in the balance it achieves between efficacy, safety, and convenience. Oral administration eliminates the need for injections or infusions, improving patient adherence[5]. Disease-specific immune modulation is made possible by its tailored method, which may lessen the systemic negative consequences of widespread immunosuppression. Its therapeutic potential has been confirmed by early clinical trials, such as the pivotal ELEVATE UC 12 and ELEVATE UC 52 investigations, which showed notable improvements in clinical remission and endoscopic healing when compared to placebo. Therefore, the creation of selective S1P receptor modulators like etrasimod represents a significant advancement despite our limited knowledge of the pathophysiology of immune-mediated inflammatory disorders (IMIDs) and the inadequate quality of current therapies. Etrasimod provides a unique way to selectively manage inflammation, reduce long-term consequences, and enhance patient outcomes in ulcerative colitis and other associated disorders by regulating important pathways involved in lymphocyte migration[6].

In addition to showing the therapeutic advantages of etrasimod, an S1P receptor selective modulator, the graphic illustrates the pathophysiology pathways of UC. Tight junctions that regulate permeability and a mucin layer preserve the epithelial barrier in a healthy colon. Increased permeability and enhanced absorption of luminal antigens and bacterial byproducts are the outcomes of tight junction dysfunction and reduced mucin production in UC[7].

These antigens are recognised by antigen-presenting cells (APCs), such as macrophages and activated dendritic cells in the lamina propria. TNF-α, IL-12, IL-23, IL-6, and IL-8 are pro-inflammatory cytokines released by activated macrophages that intensify immunological activation[8]. Dendritic cells deliver antigens to naïve $CD4^+$ T cells via HLA class II molecules. These cells then develop into distinct effector subsets, namely Th2 and Th17 cells[9]. Effector Th2 cells produce cytokines like IL-4, IL-5, and IL-13 that prolong inflammation, encourage eosinophil recruitment, and impede epithelial repair. Despite the involvement of natural killer T (NKT) cells and regulatory T cells (Tregs), these mechanisms are insufficient to manage the persistent inflammation of UC[10]. At this point, etrasimod begins to function as a drug. Etrasimod primarily binds to S1P receptors (S1PR1, S1PR4, S1PR5), preventing lymphocytes from entering the systemic circulation and trapping them in the lymphoid tissues. By preventing T-cell and leukocyte migration into the intestinal mucosa, etrasimod decreases the buildup of inflammatory cells

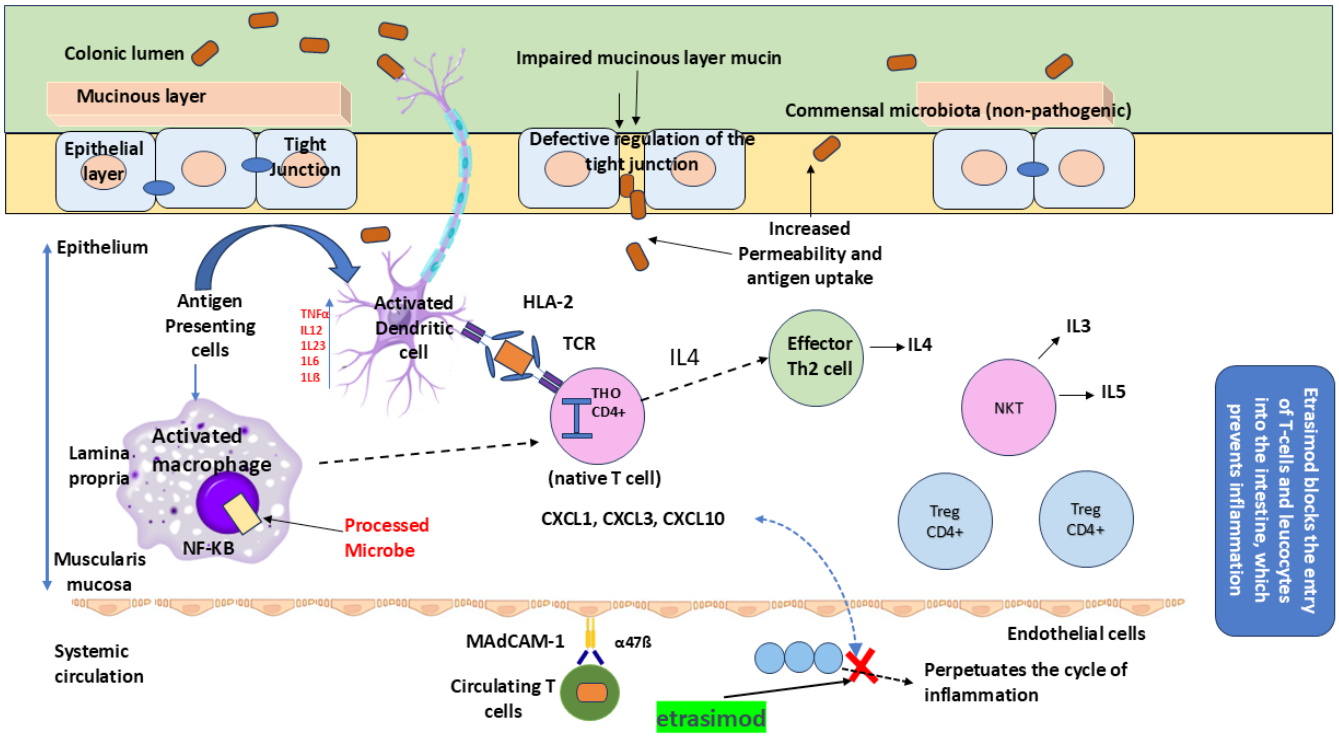
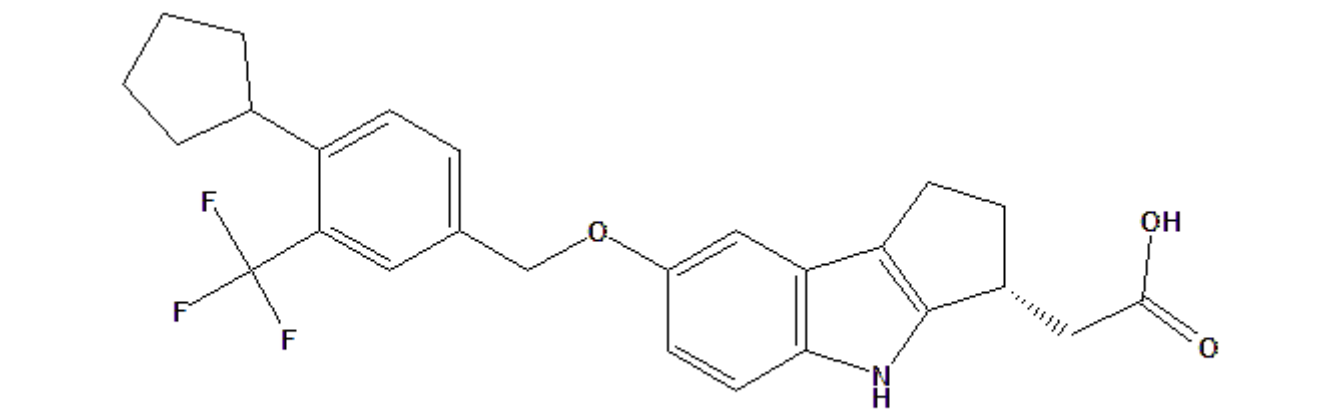


Figure 1: Pathophysiology



2-[(3R)-7-[[4-cyclopentyl-3-(trifluoromethyl)phenyl]methoxy]-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl]acetic acid

Figure 2: Structure of Etrasimod

and ends the vicious cycle of chronic inflammation, as seen in the picture [11]. The figure illustrates how etrasimod alters lymphocyte migration, restores immune balance, and reduces intestinal inflammation. While side effects like immune cell recruitment, cytokine secretion, aberrant antigen presentation, and barrier impairment are all linked to the pathophysiology of UC[12].

2. Chemistry and Pharmacokinetics

Etrasimod is a synthetic small molecule with a low molecular weight that selectively modifies sphingosine-1-phosphate (S1P) receptors. Its molecular formula is $C_{26}H_{26}F_3NO_3$, and its chemical structure is an indole acetic acid scaffold. The S1PR2 and S1PR3 subtypes, which are typically linked to off-target toxicities like cardiovascular and ocular adverse effects, are unaffected by its selective affinity for S1PR1, S1PR4, and S1PR5.This receptor profile sets etrasimod apart from prior modulators such as fingolimod, which have a higher incidence of side effects because of their wider receptor interaction[13].

Etrasimod's chemical selectivity is essential to its

efficacy as a treatment for UC. Without significantly inhibiting the immune system across the body, etrasimod lowers gastrointestinal inflammation by mainly modifying S1PR1 to limit lymphocyte migration, with a smaller function for S1PR4 and S1PR5. Its low activity at S1PR2 and S1PR3 also reduces the risk of bradycardia, macular oedema, and other cardiovascular problems linked to previous drugs[14]. Etrasimod has pharmacokinetic characteristics that make it an ideal drug for administration in the clinical environment. Following drug administration, peak plasma levels of this orally available medication are generally reached within four hours. A typical once-daily dose produces steady-state levels after seven days, allowing for a simple and predictable dosing regimen. Another key benefit for the use in patients who need drug breaks is its mean elimination half-life of around 30 hours, permitting once-daily dosing while allowing for a relatively quick washout duration on discontinuation[15]. The main cytochrome P450 enzymes involved in the metabolic process are CYP2C8, CYP2C9, and CYP3A4; CYP2C19 and CYP2J2 are less important. Oxidation, dehydrogenation, and conjugation by sulfotransferases and uridine diphosphate glucuronosyltransferases (UGTs) are the main metabolic processes. Hepatobiliary clearance is the main mode of excretion and renal clearance is not effectively utilized, as evidenced by the fact that 5% of the drug is eliminated through urine and 82% is eliminated in the faeces. Etrasimod has a volume of distribution of ~66 L and is ~98% protein-bound, indicating extensive tissue penetration. Notably, the pharmacokinetics of etrasimod are not influenced by food intake and thus do not need to be taken with meals. Etrasimod allows for clinical use and enhances compliance with the patient, as it does not need dosage adjustments during initiation of treatment, unlike certain other S1P receptor modulators[16].

The benefits of etrasimod as a next-generation S1P receptor modulator are highlighted by its combination of pharmacokinetic and chemical characteristics. Its rapid pharmacokinetics, short washout time, and once-daily oral dosage make it a handy and patient-friendly choice, and its structural specificity reduces off-target effects. These characteristics offer a solid basis for its application in the management of ulcerative colitis and maybe other inflammatory conditions mediated by the immune system[17].

3. Mechanism of Action

A predominance of pro-inflammatory immune mechanisms over control pathways is responsible for the pathogenesis of UC, culminating in chronic mucosal injury and effector T cell activation. The migration of lymphocytes from lymphoid tissues into the bloodstream and eventually into the inflamed intestinal mucosa plays a vital role in this imbalance of immunity. One of the therapeutic approaches to decreasing mucosal inflammation with minimal interference with systemic immunity is to modulate this migratory process[18].

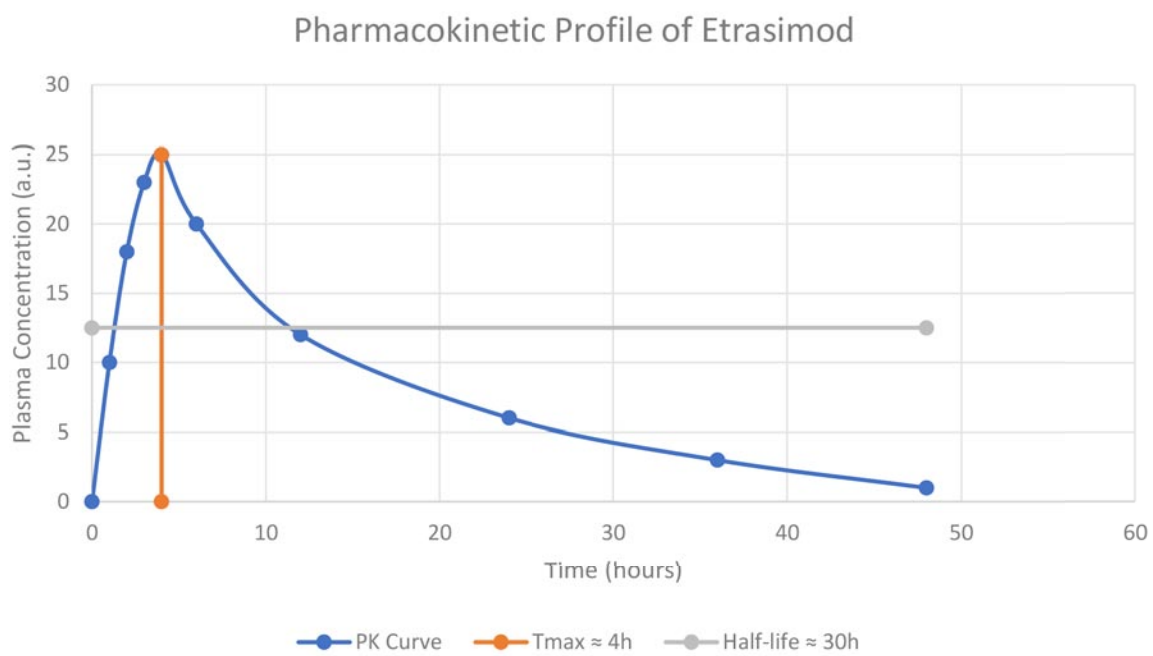


Figure 3: Pharmacokinetic Profile of Etrasimod

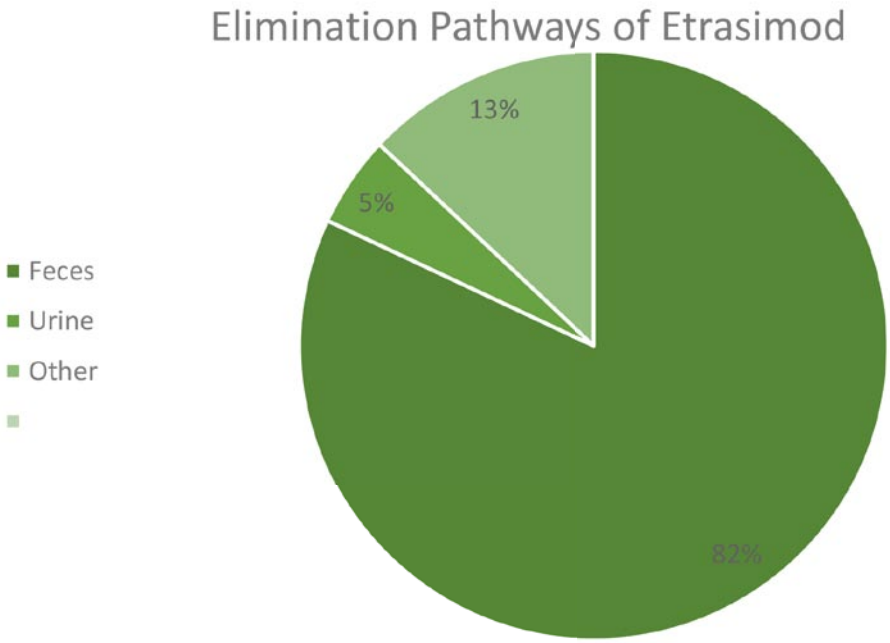


Figure 4: Elimination pathways of etrasimod

The regulation of lymphocyte departure from lymph nodes is mostly dependent on the sphingosine-1-phosphate (S1P) signalling pathway. Five different kinds of G-protein-coupled receptors (S1PR1–5) are bound by the bioactive lipid S1P. S1PR1 is the most crucial of them for directing lymphocytes into the circulation via gradients in S1P concentration. S1PR1 inhibition interferes with this gradient detection, which causes lymphocytes to gather in secondary lymphoid organs and less infiltration into inflammatory regions. While S1PR5 is involved in the migration of natural killer (NK) cells and the immunological surveillance of the central nervous system, S1PR4 is linked to the activities of dendritic cells and Th17 cells[19].

Etrasimod does not act on the S1PR2 and S1PR3 subtypes responsible for pulmonary and cardiovascular adverse effects but selectively acts on S1PR1, S1PR4, and S1PR5. Its activity as a functional antagonist of S1PR1 blocks lymphocytic movement by inducing receptor internalisation and degradation. After two weeks, this leads to a reduction of 40–50% in the levels of circulating lymphocytes, a change that can be reversed once the treatment is discontinued. Etrasimod interferes with the inflammatory process seen in ulcerative colitis by reducing lymphocyte infiltration in the colonic mucosa[20].

Etrasimod also possesses other immunomodulatory activities beyond sequestration of lymphocytes. Preclinical evidence suggests that the modulation of S1PR4 and S1PR5 can affect dendritic cell activity, chemokine signalling, and cytokine release, thus extending its anti-inflammatory activity. In addition, etrasimod might contribute to the restoration of the integrity of the intestinal epithelial barrier in order to protect against bacterial migration and ensure mucosal homeostasis. Thus, etrasimod addresses the immunological dysregulation and barrier dysfunction underlying UC[21].

The reversibility of Etrasimod's mechanism is one of its unique characteristics. The long-term danger of immunological insufficiency is decreased because, unlike cytotoxic or immunosuppressive medications, lymphocyte counts revert to normal within days after quitting the treatment. Crucially, etrasimod successfully strikes a balance between therapeutic immune modulation and host defence preservation, as evidenced by the lack of a discernible rise in severe or opportunistic infections during clinical studies when compared to placebo[22].

Etrasimod has a more specific mechanism of action than other therapies targeting immunological mechanisms in ulcerative colitis, including TNF-α inhibitors or Janus kinase (JAK) inhibitors. JAK inhibitors target multiple signalling pathways with broad effects, and biologics have the common effect of reducing inflammatory cytokines. In contrast, etrasimod reduces specifically gut inflammation while preserving general immune function through direct influence on lymphocyte trafficking[23].

Etrasimod selectively acts on S1PR1, S1PR4, and S1PR5 to affect the behaviour of immune cells. This leads to increased epithelial barrier integrity,

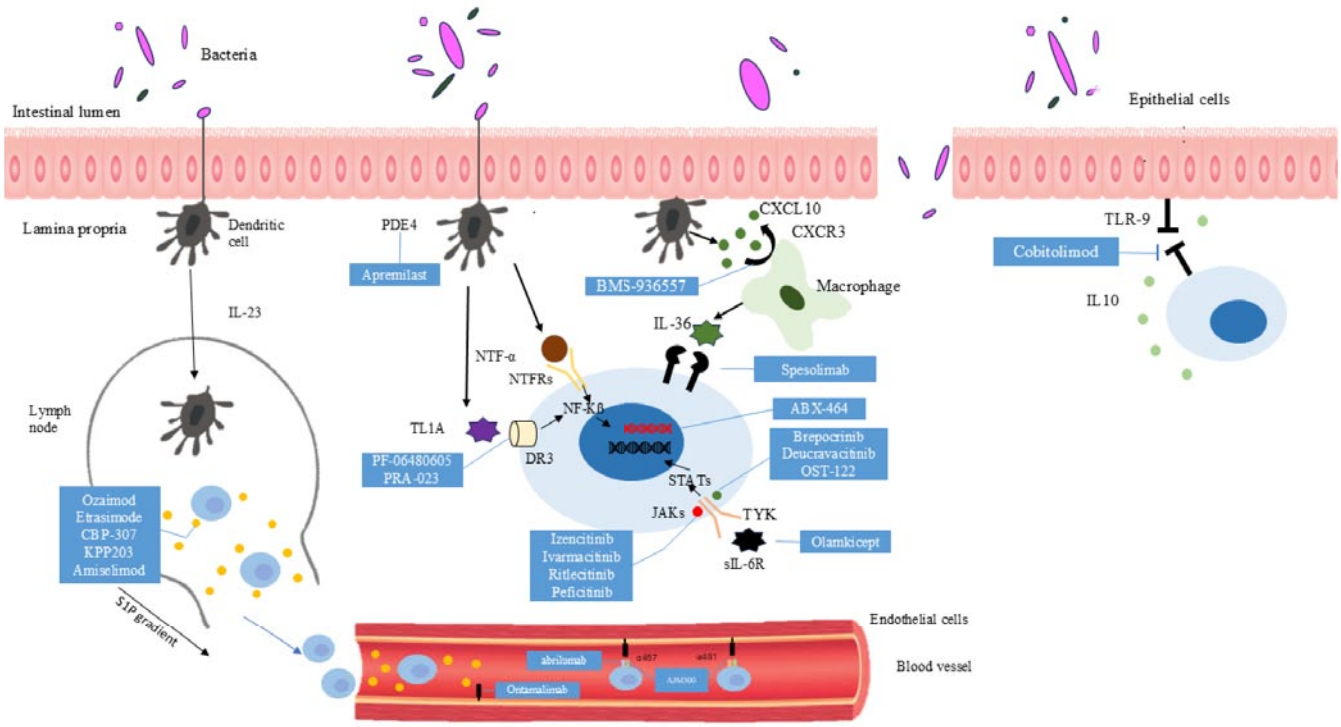


Figure 5: Elimination pathways of etrasimod

Table 1: Current and potential clinical indications of etrasimod with corresponding trial status.

Indication	Status
UC	Approved (FDA, 2023)
Crohn's disease (CD)	Phase II/III trials are ongoing
Atopic dermatitis	Phase II/III trials are ongoing
Eosinophilic esophagitis	Phase II trials are ongoing
Systemic lupus erythematosus (exploratory)	Exploratory/early research
Multiple sclerosis (exploratory)	Exploratory/early research

decreased mucosal infiltration, and lymphocyte retention in lymph nodes. As a result of its reversible and selective action, it is an attractive treatment option for those with moderate to severe ulcerative colitis, as opposed to more general immunosuppressants and less specific S1P modulators[24].

4. Clinical Indications and Therapeutic Uses

The main purpose of etrasimod, a pill-based modulator of the sphingosine-1-phosphate (S1P) receptors, has been to treat UC, although it may also be used to treat several immune-mediated inflammatory diseases. By binding specifically to S1PR1, S1PR4, and S1PR5, etrasimod affects lymphocyte migration and lowers mucosal inflammation, providing a new therapeutic class that may be used in conjunction with small molecules and current biologics[25].

Ulcerative Colitis

The initial clinical use of etrasimod is in patients with moderate to severe ulcerative colitis. UC patients are often plagued with therapeutic difficulties: corticosteroids are of transient benefit, aminosalicylates are less helpful in more active disease, and biologics like TNF inhibitors or anti-integrin monoclonal antibodies are hindered by immunogenicity, variable durability of response, and parenteral dosing requirements. These problems are reduced by etrasimod, an oral drug with a targeted mechanism of action[26].

When compared to a placebo, etrasimod significantly improved clinical remission, mucosal healing, and rates of steroid-free remission in the crucial ELEVATE UC 12 and ELEVATE UC 52 phase 3 trials. Notably,

improvements were seen in both biologic-naïve patients and those who had previously failed Janus kinase (JAK) inhibitors or other biologics. Its use for long-term illness care is further supported by its once-daily oral administration and lack of a titration regimen. Etrasimod was approved by the FDA in 2023 to treat individuals with moderately to severely active ulcerative colitis in light of these findings[26,27].

Crohn's Disease

Although most clinical research has been on UC, estrasimod is also being closely examined for treatment in Crohn's disease (CD). Like UC, CD is brought on by abnormal immune cell trafficking, and one treatment option is to modify sphingosine-1-phosphate (S1P). Ongoing phase II/III trials are investigating its potential in patients with severe to moderate CD with the goals of enhancing remission rates, endoscopic findings, and overall quality of life. If successful, etrasimod may emerge as one of the first oral small molecules to offer sustained treatment solutions for both primary types of inflammatory bowel disease (IBD)[28].

Atopic Dermatitis and Eosinophilic Esophagitis

Etrasimod is being researched for treatment in several other chronic inflammatory diseases in addition to IBD. Phase II trials indicate that by affecting lymphocyte mobility and changing the cytokine profile, it may successfully lessen skin inflammation and irritation in atopic dermatitis. With phase II studies still underway, etrasimod showed promise in lowering eosinophilic infiltration in the oesophagus and alleviating clinical symptoms for eosinophilic esophagitis[29].

Broader Potential in IMIDs

Because of its mechanism of action, etrasimod could have an important application in the treatment of systemic autoimmune disorders such as multiple sclerosis (MS) and systemic lupus erythematosus (SLE), though this is still in the experimental phase. Unlike fingolimod, the initial approved S1P modulator for MS, which is related to bradycardia, retinal oedema, and long washout duration, etrasimod is safer due to its selectivity and extremely short half-life[30].

Position in Therapy

Etrasimod is becoming a first-line advanced therapy for UC when standard drugs have failed, particularly for individuals who are contraindicated for biologics or prefer oral therapies. Alongside JAK inhibitors and biologics, it offers benefits in terms of administration and washout flexibility because of its advantageous mix of efficacy, tolerability, and ease. Etrasimod may develop into a complete therapy option for chronic inflammatory illnesses as clinical trial data for Crohn's disease (CD) and other IMIDs grow[31].

5. Clinical Trial Evidence

The outcomes of the primary ELEVATE UC trials, which assessed etrasimod's safety and effectiveness in patients with moderate-to-severe UC, have had a major impact on the medication's clinical development. These trials offer a substantial body of evidence in favor of its approval and integration into treatment plans when paired with earlier phase investigations[32].

ELEVATE UC 12

A phase 3 randomised, double-blind, placebo-controlled trial named the ELEVATE UC 12 trial was conducted to assess etrasimod as an induction therapy for 12 weeks. Patients could be included if they had moderately to severely active UC with a modified Mayo score of 4–9, an endoscopic subscore of ≥2, and a rectal bleeding subscore of ≥1. Participants in the study were those who had never received biologics or JAK inhibitors before, and those who had.

The outcomes showed that at week 12, 25% of etrasimod-treated patients attained clinical remission, while just 15% did among those who received the placebo. Etrasimod also markedly enhanced endoscopic response, histologic remission, and health-related quality-of-life scores, which were all considered to be useful secondary outcomes. These data demonstrate the ability of the drug to achieve objective mucosal healing in addition to symptom relief[33].

The ELEVATE UC 52 trial employed a treat-through design and was categorised as phase 3. The trial incorporated a 12-week induction period and a maintenance phase of 40 weeks. This design makes it possible to gauge both the short-term and long-term effectiveness[34].

By week 12, 27% of patients who were administered etrasimod experienced clinical remission, compared to a mere 7% of those who received a placebo. By week 52, remission rates were 32% among etrasimod users and remained at 7% among the placebo. Moreover, a substantially larger percentage of patients demonstrated endoscopic improvement, mucosal healing with histologic remission, and could sustain corticosteroid-free remission. Notably, treatment benefit was seen irrespective of prior exposure

to biologic or JAK inhibitors, demonstrating the effectiveness of etrasimod across a large population of patients[35].

Safety Outcomes

Etrasimod showed a good safety profile in both investigations. Headache, anaemia, and UC flare-ups were among the mild to moderately severe side effects that were most often reported. There was no discernible rise in severe infections or malignancies as compared to a placebo, and nine cases of bradycardia or sinus bradycardia were reported; all of these cases resolved on their own. Etrasimod's versatility for clinical application was increased by the fact that it did not require dosage titration and had a shorter washout period than ozanimod[36].

Other Clinical Programs

Etrasimod is being studied for immune-related disorders other than ulcerative colitis. Phase II/III studies for eosinophilic esophagitis, atopic dermatitis, and Crohn's disease are currently in progress, demonstrating the drug's wider potential. According to preliminary research, its capacity to control lymphocyte migration may provide therapeutic advantages in a range of chronic inflammatory conditions[37].

Clinical Significance and Perception

The findings from the ELEVATE program show etrasimod to be an effective once-daily oral therapy in patients with UC, including those who have already been treated with biologics or JAK inhibitors. The convenience of once-daily dosing orally, quick onset, and brief half-life provides major benefits compared with parenteral biologics and ozanimod, which necessitate dose escalation[38].

Clinical evidence is in favour of the use of etrasimod for the treatment of UC as both induction and maintenance therapy. Etrasimod stands to be a welcome addition to the currently available treatment options for moderate-to-severe UC and holds potential for other immune-mediated diseases currently in development, based on its consistent efficacy across different endpoints and tolerable safety profile[39].

6. Safety Profile and Adverse Effects

Phase II and III clinical trials, including the ELEVATE UC 12 and ELEVATE UC 52 studies, have delineated etrasimod's safety profile. Overall, etrasimod had a positive risk-benefit ratio, with all adverse events being of mild to moderate severity and appearing in rates similar to placebo. Common treatment-emergent adverse events were headache, anaemia, and worsening of symptoms of ulcerative colitis; these events were generally self-limiting and did not necessitate drug discontinuation. The frequency of upper respiratory tract infection, nasopharyngitis, and gastrointestinal infection was also similar between the etrasimod and placebo groups[40].

Cardiac Safety

Etrasimod can affect cardiac conduction, as do other S1P receptor modulators. During clinical trials, nine cases of bradycardia or sinus bradycardia were reported in patients taking etrasimod, and none were noted in the group receiving placebo. The vast majority of the events were asymptomatic and spontaneously resolved. Two symptomatic cases led to trial discontinuation, though none were life-threatening. Significantly, etrasimod's enhanced receptor selectivity and pharmacokinetic profile imply that it does not need dose adjustment or first-dose cardiac monitoring, in contrast to fingolimod[41].

Although clinical effects have been uncommon, a few patients have exhibited evidence of aberrant, prolonged atrioventricular (AV) conduction intervals. Precaution is advised in those with underlying conduction abnormalities or those taking beta-blockers or calcium channel blockers concurrently[42].

Table 2: Adverse Events: Etrasimod vs. Placebo

Adverse Event	Etrasimod	Placebo
Headache	Common, mild	Common
Anemia	Mild, reversible	Mild
Bradycardia / Sinus bradycardia	Rare, mostly asymptomatic	None
UC flare	Reported, self-limited	Reported
Upper respiratory tract infection	Similar to a placebo	Similar rates
Macular oedema (rare)	Very rare, reversible	Not reported
Elevated liver enzymes	Occasional, not clinically significant	Not significant

Ocular Events

There have been occasional reports of macular oedema, a recognised first-generation S1P modulator side effect, with etrasimod. Upon discontinuation of the drug, the few minor instances that have been reported may resolve. Though routine eye exams are not necessary, those with pre-existing retinal diseases or diabetes can be monitored more closely[43].

Lower peripheral lymphocyte counts linked to S1P regulation raise concerns about susceptibility to infections. However, throughout clinical studies, etrasimod and placebo groups had comparable rates of opportunistic infections, severe infections, and total infections. There were no cancer cases or fatalities from therapy. This implies that etrasimod could be different from other general immunosuppressants, as it suppresses gut inflammation without compromising immune surveillance[44].

Other Adverse Events

Slight elevations in liver enzymes and transient gastrointestinal side effects have been recorded, but were normally not clinically significant. In the trial programs, no long-term signs of damage to the kidneys, lungs, or nervous system were seen[45].

Comparison with Other S1P Modulators

The safety profile of Etrasimod is better compared to other drugs in its class. The first-generation modulators, like tingolimod, are known to have greater risks of macular oedema, bradycardia, AV block, and prolonged washout duration. Another selective modulator, ozanimod, also carries an active metabolite responsible for drug-drug interactions and needs dosage up-titration to counteract the risk of bradycardia. As opposed to this, Etrasimod is said to be more clinically beneficial because of its shorter half-life, not requiring titration, and fewer off-target effects[46].

Clinical Implications

Etrasimod demonstrates a favourable safety profile compared with earlier S1P modulators. Upon withdrawal, side effects associated with it tend to reverse, are predictable, and can be controlled. Although etrasimod shows a sound safety profile appropriate for long-term administration in the majority of patients, clinicians should be cautious with patients who possess eye-related risk factors or pre-existing cardiovascular diseases[47].

7. Pharmacological Advantages Over Other S1P Modulators

Since the launch of fingolimod, the initial drug of this class, there has been a major disruption in the therapeutic class of sphingosine-1-phosphate (S1P) receptor modulators. Etrasimod is a more recent drug that offers evident improvements compared with previous modulators by having improved receptor selectivity in combination with an acceptable pharmacokinetic and safety profile[48].

Receptor Selectivity

Being a first-generation non-selective modulator, tingolimod binds to S1PR1, S1PR3, S1PR4, and S1PR5. Its binding at S1PR3 is associated with several cardiovascular and respiratory toxicities such as bradycardia, AV block, and hypertension. Contrary to this, etrasimod has minimal activity on S1PR2 and S1PR3 but is highly selective for S1PR1, S1PR4, and S1PR5. This selective binding pattern modulates lymphocyte trafficking so that therapeutic effectiveness is ensured with decreased chances of cardiac and ocular side effects[49].

The second-generation modulator Ozanimod mainly targets S1PR1 and S1PR5, bypassing S1PR2 and S1PR3. In contrast, etrasimod impacts S1PR4, which is crucial for the operation of Th17 and dendritic

Table 3: Comparison of S1P Receptor Modulators

Property	Fingolimod	Ozanimod	Etrasimod
Receptor selectivity	S1PR1, S1PR3, S1PR4, S1PR5 (non-selective)	S1PR1, S1PR5	S1PR1, S1PR4, S1PR5 (highly selective)
Half-life	~6–9 days	~19–21 h (parent), 10–13 days (active metabolite)	~30 h
Need for dose titration	Yes	Yes (7-day titration)	No
Washout period	Weeks	Several weeks (due to metabolite)	~1 week
Key safety concerns	Bradycardia, AV block, macular oedema, infections	Bradycardia (first dose), drug–drug interactions	Mild bradycardia (rare), headache, anaemia

cells, in addition to targeting these receptors. With a safe profile, this increased selectivity might result in improved immunomodulatory effects[50].

Etrasimod is appropriate for clinical usage due to a number of its pharmacokinetic characteristics. It's about 30-hour mean half-life enables a once-daily oral dosage and sufficient washout within a week after treatment cessation. Fingolimod, on the other hand, has a half-life of more than six days, which means that immunosuppression lasts long after the course of therapy is over[51].

While ozanimod also has a relatively short duration of action compared to fingolimod, it requires more extensive washout periods and also poses a higher risk of drug-drug interaction with its metabolism to an active metabolite with a 10–13-day half-life. Etrasimod, on the other hand, offers more consistent pharmacokinetics and evades this concern by not having long-lasting metabolites[52].

Another significant benefit of starting etrasimod is that it does not need titration of doses. To avoid first-dose bradycardia, which may complicate starting the medication and discourage adherence, ozanimod needs titration on a seven-day schedule. Etrasimod can be given readily in both inpatient and outpatient settings because it may be initiated at the full therapeutic dose[53].

Safety and Tolerability

The enhanced receptor selectivity and pharmacokinetics of etrasimod are also evident from its safety profile. In contrast to fingolimod, etrasimod is not linked to protracted bradycardia, notable AV block, or high rates of macular oedema. Clinical trials record adverse events at a similar rate to placebo, with no opportunistic infections or malignancy signal. The reduced half-life also diminishes long-term immune suppression concerns, one of the major limitations of fingolimod[54].

Clinical Convenience

From a patient's perspective, etrasimod offers many useful benefits:

There is no need for injections or infusions when the drug is taken orally.

Treatment beginning is made easier by the lack of titration.

Greater flexibility in the event that therapy must be stopped owing to infection, surgery, or pregnancy planning is made possible by a shorter washout time.

Compared to biologics, which need cold-chain storage, it is more convenient to store the drug at room temperature[55].

8. Drug Interactions and Contraindications

The clinical use of etrasimod necessitates careful evaluation of possible drug interactions and certain contraindications in individual patients, as with other sphingosine-1-phosphate (S1P) receptor modulators. Although etrasimod is generally well tolerated, specific comorbidities and concomitant medications may increase attendant risks[56].

Drug Interactions

Etrasimod is mostly metabolised by the cytochrome P450 (CYP) enzyme system, namely CYP2C8, CYP2C9, and CYP3A4. As a result, the concomitant administration with potent inhibitors or inducers of these enzymes can change the levels of the drug[57].

Gemfibrozil, fluconazole, and ketoconazole are examples of CYP inhibitors that may enhance exposure to etrasimod and raise the possibility of adverse effects. However, CYP inducers including rifampin, carbamazepine, and phenytoin may diminish the drug's level and efficacy[58].

Because of its effect on cardiac function, etrasimod should be used concomitantly with other agents that reduce heart rate or prolong atrioventricular (AV) conduction, including beta-blockers, non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem), digoxin, or Class Ia/III antiarrhythmics. The combination of these drugs may enhance the risk of developing symptomatic bradycardia or AV block[59].

Also, caution must be exercised when administering drugs that cause QT prolongation since S1P modulation could affect cardiac conduction. While no clinical trials indicated marked QT prolongation, additive effects cannot be entirely ruled out[60].

Contraindications

In some populations, etrasimod is to be avoided when the risk exceeds the possible benefit: Severe hepatic impairment (Child-Pugh class C), resulting in decreased metabolism, can lead to enhanced systemic exposure. In general, dosage adjustments are not required in patients with mild to severe liver disease. Patients with unstable angina, decompensated heart failure, recent myocardial infarction, or serious AV block should see a cardiologist before the administration of etrasimod. Alteration of S1P receptors in pregnancy and lactation can be harmful to the developing embryo. Female patients of childbearing age are cautioned to use an

effective form of contraception during therapy and for a minimum of 14 days following discontinuation of therapy. Breastfeeding is contraindicated because of the risk of drug transfer into breast milk. Hypersensitivity: Patients with a history of etrasimod or its ingredients, to which they are sensitive, should not receive it[61].

Special Considerations

People with pre-existing eye disorders (such as diabetic retinopathy or uveitis) should have a comprehensive eye exam as a baseline since they may be more susceptible to macular oedema. Although pulmonary toxicity is less prevalent with etrasimod than with fingolimod, patients with chronic lung problems should be closely watched for it. In contrast to fingolimod or ozanimod, side effects and drug interactions disappear rapidly after stopping the medication; therefore, the comparatively short half-life of around 30 hours and the absence of active metabolites are beneficial. Additionally, this feature makes it possible to plan for pregnancy or manage surgery with more flexibility[62].

9. Conclusion

Etrasimod is a selective S1P receptor modulator that has been shown to be effective in treating ulcerative colitis and may find use in other IMIDs. It differs from previous medicines and biologics due to its favorable safety profile, oral once-daily dose, and quick washout. Its therapeutic role may be expanded by further studies. To determine the ideal function of etrasimod in treatment algorithms, more long-term and comparative research is required.

Authors' Contribution

M.R.K. and A.S.S. conceptualised the study. A.S.S. supervised the work. B.R.I., H.S.G., and N.D.P. contributed to data analysis and figure preparation. R.K.P. assisted in literature review and manuscript formatting. All authors reviewed and approved the final manuscript.

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Conflict of Interest

The authors gratefully declare that they have no conflicts of interest.

Statements and Declarations

No financial or non-financial competing interests exist. No human or animal subjects were involved in this study.

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