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Ponesimod: A review of pharmacology, clinical efficacy, and safety in multiple sclerosis treatment

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Abstract
Ponesimod is an oral, selective sphingosine-1-phosphate receptor 1 (S1P1) modulator that has been approved for the treatment of relapsing forms of multiple sclerosis (RMS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive multiple sclerosis. As a member of the sphingosine-1-phosphate modulator class, Ponesimod exerts its therapeutic effects by selectively binding to the S1P1 receptor, leading to internalization and degradation of the receptor. This functional antagonism results in the sequestration of lymphocytes within lymph nodes, thereby reducing their migration into the central nervous system and limiting inflammatory damage associated with MS relapses.

Ponesimod offers several pharmacokinetic advantages over earlier agents in the same class, such as a shorter half-life and greater receptor selectivity, which may translate into a more favorable safety and tolerability profile. Clinical efficacy has been demonstrated in the phase III OPTIMUM trial, which showed significant reductions in the annualized relapse rate, MRI lesion burden, and fatigue symptoms when compared to teriflunomide. The drug also has a rapid onset and offset of action, which provides clinicians with greater flexibility in managing therapy interruptions or transitions.

This review provides a comprehensive overview of Ponesimod's mechanism of action, pharmacokinetics, efficacy in clinical trials, safety considerations, and its place within the current landscape of disease-modifying therapies for MS.

Keywords: Ponesimod, S1P1 receptor modulator, Multiple sclerosis (MS), relapsing forms, pharmacokinetics, OPTIMUM trial

Introduction
Multiple sclerosis (MS) is a chronic autoimmune disease affecting the central nervous system. Sphingosine-1-phosphate (S1P) receptor modulators have emerged as effective treatments. Ponesimod is a newer, selective S1P1 receptor modulator that offers a favorable pharmacological profile and promising clinical efficacy [1].

Ponesimod is a selective modulator of the sphingosine 1-phosphate receptor 1 (S1P1), approved for the treatment of relapsing forms of multiple sclerosis in adults. It was developed to provide a more targeted alternative to fingolimod, which also affects sphingosine 1-phosphate receptor 3 (S1P3)-a factor believed to contribute to some of its side effects. As a result, more selective agents like ponesimod were created to minimize these issues [2].

Mechanism of action
Ponesimod binds selectively to the S1P1 receptor, causing internalization and degradation of the receptor. This prevents lymphocytes from exiting lymph nodes, thereby reducing their migration to the central nervous system and limiting the inflammatory processes characteristic of MS. The sphingosine 1-phosphate receptor 1 (S1P1R) is found on the surface of lymphocytes and is capable of detecting sphingosine 1-phosphate (S1P) at very low, nanomolar concentrations. S1P is derived from the breakdown of sphingomyelin, a component of cell membranes. As sphingomyelin degrades, lymphocytes are guided by S1P concentration gradients through S1P1R activation. They exit lymphoid tissues in response to higher S1P levels present in the blood and lymph. Ponesimod interferes with this process by activating and internalizing S1P1R on lymphocytes, making them unresponsive to S1P gradients and thereby lowering their presence in the bloodstream. Notably, ponesimod is approximately 650 times more selective for S1P1R than S1P itself [3-4].

Pharmacokinetics

Absorption

Ponesimod exposure increases proportionally with doses ranging from 1 to 75 mg per day. Peak plasma concentrations are typically reached within 2 to 4 hours after dosing. When a 10 mg dose is taken orally, the drug shows an absolute bioavailability of 83.8%. The presence of food does not significantly impact the pharmacokinetics of ponesimod.

Distribution

In healthy individuals, the steady-state volume of distribution after intravenous administration is 160 liters. Ponesimod demonstrates extensive binding to plasma proteins, with over 99% bound.

Metabolism

Ponesimod undergoes extensive metabolism in the body, although the unchanged form remains the primary component in the bloodstream. Two inactive metabolites, M12 and M13, have been detected in human plasma, contributing approximately 6% and 20%, respectively, to overall drug exposure. The conversion of ponesimod to M13 primarily involves non-CYP450 enzymes, while both CYP450 enzymes (including CYP2J2, CYP3A4, CYP3A5, CYP4F3A, and CYP4F12) and non-CYP450 enzymes are involved in the formation of M12. Additionally, ponesimod is directly glucuronidated, primarily by UGT1A1 and UGT2B7.

Elimination

Following a single intravenous dose, ponesimod has a total clearance of 3.8 liters per hour. The drug has an elimination half-life of approximately 33 hours when taken orally [5].

Pharmacodynamics

Ponesimod is a modulator of the sphingosine 1-phosphate receptor 1 (S1P1) used for the treatment of relapsing forms of multiple sclerosis in adults. It offers a prolonged effect, allowing for once-daily dosing. Patients should be informed of potential risks, including infections, slowed heart rate, atrioventricular conduction delays, reduced lung function, liver damage, elevated blood pressure, skin cancers, harm to the fetus, and macular edema [5].

Absorption

A 10mg oral dose of ponesimod is 84% bioavailable. Ponesimod reaches a C_{max} of 109 ng/mL, with a T_{max} of 4.0 hours, and an AUC of 3872 h*ng/mL.[5].

Efficacy

The phase III OPTIMUM trial demonstrated that Ponesimod significantly reduced the annualized relapse rate (ARR) compared to teriflunomide. The drug also showed benefits in MRI lesion count and fatigue symptoms. The ARR was reduced by 30.5% in the Ponesimod group [5].

Safety and Tolerability

Ponesimod was generally well tolerated. Common side effects include headache, nasopharyngitis, and liver enzyme elevations. Cardiac side effects like bradycardia were minimized through a gradual dose titration schedule.

Toxicity

In cases of overdose, patients may exhibit symptoms such as a slowed heart rate (bradycardia), atrioventricular (AV) conduction block, and fluctuations in blood pressure. Monitoring should include pulse rate, blood pressure, and electrocardiograms (ECGs). Management involves symptomatic and supportive care, with treatments like atropine potentially used to address bradycardia. Dialysis is unlikely to effectively eliminate the drug from the bloodstream [5].

Uses

Multiple sclerosis - Ponesimod is prescribed for adults to treat relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting MS, and active secondary progressive MS [6].

Administration

Take ponesimod by mouth once daily, with or without food. Tablets should be swallowed whole-do not chew or crush them [6].

Storage

Keep ponesimod tablets in their original packaging and store them at a temperature between 20-25°C, allowing for short-term variations between 15-30°C [7].

Comparison with other therapies

Compared to other S1P modulators like fingolimod and ozanimod, Ponesimod has improved receptor selectivity and a shorter half-life. These features reduce long-term safety concerns and make it easier to manage adverse events or therapy interruption [7].

Clinical perspective

Ponesimod is among the disease-modifying treatments available for managing relapsing forms of multiple sclerosis (MS) [8].

The American Academy of Neurology (AAN) advises that disease-modifying therapies should be offered to individuals with relapsing forms of multiple sclerosis (MS) who have experienced recent relapses or show active lesions on MRI scans. However, the experts note that the potential benefits versus risks-such as side effects or the challenges of long-term medication use-are unclear for patients who have been relapse-free for two or more years and show no active MRI findings. When choosing a suitable disease-modifying treatment, healthcare providers should consider factors such as side effects, tolerability, route of administration, safety, effectiveness, cost, and the patient's personal preferences. Since damage to the central nervous system (CNS) begins early and progresses throughout the course of multiple sclerosis (MS), some healthcare professionals advocate for starting disease-modifying therapy promptly after diagnosis and maintaining it long-term. Treatment should continue unless it proves clearly ineffective, causes intolerable side effects, the patient cannot comply with the treatment plan, or a more suitable therapy becomes available [9].

Discussion

The therapeutic value of Ponesimod in managing relapsing forms of multiple sclerosis (MS) has been extensively evaluated, most notably in the phase III OPTIMUM trial. This pivotal clinical study enrolled over 1,100 patients and directly compared Ponesimod with teriflunomide, a widely used oral

disease-modifying therapy (DMT) for MS. The primary outcome demonstrated a statistically significant reduction in the annualized relapse rate (ARR) by 30.5% in the Ponesimod group compared to teriflunomide. Additionally, MRI findings indicated a notable reduction in T2 lesion volume and gadolinium-enhancing lesions, underscoring the drug's effect on reducing central nervous system inflammation.

From a pharmacodynamic and pharmacokinetic perspective, Ponesimod's short half-life (~33 hours) and high selectivity for the S1P1 receptor distinguish it from earlier S1P modulators such as fingolimod. This specificity reduces off-target effects, including cardiovascular and hepatic complications that have been linked with less selective agents. Importantly, its shorter half-life allows for greater flexibility in treatment management, especially in scenarios requiring therapy interruption or transition.

Ponesimod's pharmacokinetic profile supports once-daily oral dosing with minimal impact from food intake, which enhances patient adherence. After a 10 mg oral dose, the drug reaches Cmax within 4 hours, with an absolute bioavailability of 84%. It undergoes both CYP450 and non-CYP450 metabolism, leading to two major inactive metabolites (M12 and M13), which contribute to its overall safety profile.

Regarding tolerability and safety, Ponesimod was generally well accepted by patients. The most common adverse events included headache, nasopharyngitis, and mild hepatic enzyme elevations. Cardiovascular risks, such as bradycardia and atrioventricular conduction delays, were mitigated through a gradual 14-day dose titration schedule. These findings emphasize that careful initiation protocols can minimize first-dose effects often observed with S1P receptor modulators.

In terms of comparative efficacy, Ponesimod offers meaningful advantages over other agents in the same class. Fingolimod, for instance, affects multiple S1P receptor subtypes, which increases the risk of systemic side effects. Meanwhile, Ozanimod, though selective, has a longer half-life than Ponesimod, potentially limiting its flexibility in clinical scenarios. As such, Ponesimod's receptor specificity and reversible pharmacology are favorable attributes, particularly for patients with concerns about long-term immunosuppression or treatment discontinuation.

From a clinical practice standpoint, current guidelines by the American Academy of Neurology (AAN) recommend early initiation of DMTs in patients with active relapsing MS. Ponesimod aligns with this approach by offering a treatment that is both effective and manageable, especially for individuals with active disease seeking an oral therapy with a lower risk of immune-related complications.

Overall, the evidence suggests that Ponesimod is a valuable addition to the armamentarium of MS therapies. Its favorable efficacy, safety, and tolerability profile, combined with pharmacokinetic advantages, positions it as a strong candidate for first-line therapy in many patients with relapsing forms of MS [10].

Conclusion

Ponesimod represents a significant advancement in the treatment of relapsing forms of multiple sclerosis. With robust efficacy data demonstrated in clinical trials and a well-characterized safety profile, it provides clinicians with an effective and manageable therapeutic option. Its high selectivity for the S1P1 receptor and shorter half-life offers advantages in terms of safety and treatment flexibility. These features make Ponesimod particularly suitable for patients who require a convenient oral medication with a lower risk of long-term immunosuppression and rapid reversibility upon discontinuation.

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