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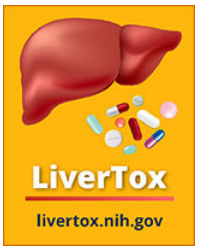
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Ponesimod

Updated: July 15, 2021.

OVERVIEW

Introduction

Ponesimod is an orally available immunomodulatory drug used to treat relapsing forms of multiple sclerosis. Ponesimod is associated with transient serum enzyme elevations during therapy but has not been linked to instances of clinically apparent liver injury with jaundice, although experience with its use has been limited.

Background

Ponesimod (poe nes' i mod) is an immunomodulatory agent used in the treatment of multiple sclerosis that is believed to act by modulating sphingosine-1-phosphate (S1P) receptors. Ponesimod is an analogue of sphingosine and related in structure to fingolimod, the first S1P receptor modulator approved for use in multiple sclerosis. While fingolimod demonstrates nonspecific S1P receptor binding (subtypes 1, 3, 4 and 5), ponesimod has a more limited specificity and primarily blocks S1P receptor-1 activity. The S1P receptor modulators, once phosphorylated intracellularly, render T and B cells insensitive to signals necessary for egress from lymphoid tissue. In animal models of multiple sclerosis, ponesimod resulted in reduced recirculation of autoaggressive lymphocytes to the central nervous system. Subsequently, in several randomized controlled trials, ponesimod was shown to reduce relapse rates and improve neuro-radiologic outcomes in adult patients with relapsing multiple sclerosis. Ponesimod was approved for use in the United States in 2021 as therapy of relapsing multiple sclerosis in adults. It is available in tablets of 2 to 10 mg for dose initiation and 20 mg for maintenance therapy under the brand name Ponvory. As with other S1P receptor modulators, a period of dose escalation (14 days) is recommended for initiation of therapy with ponesimod. Ponesimod has also been shown to have beneficial effects in plaque psoriasis, but has yet to be approved for that indication. Common side effects of ponesimod (as with most S1P receptor modulators) are lymphopenia, headache, dizziness, diarrhea, cough, rhinorrhea, peripheral edema and back and abdominal pain. Rare, but potentially severe adverse events include severe viral, bacterial or fungal infections, atrial arrhythmias and bradycardia, macular edema, decrease in pulmonary function, progressive multifocal leukoencephalopathy (PML), and embryonal-fetal toxicity. Patients on long term ponesimod should be monitored for infectious complications and for cardiac, pulmonary and ophthalmologic status.

Hepatotoxicity

In preregistration trials of ponesimod, serum ALT elevations were common (in up to 23% of recipients) but were typically mild and asymptomatic, returning to baseline values even with continuation of therapy or within a few months of stopping. In one prospective, carefully monitored trial, serum aminotransferase elevations above 3 times upper limit of normal (ULN) were reported in 17% of ponesimod recipients and above 5 times ULN in

4.6%. In these prelicensure clinical trials, there were no cases of acute hepatitis or clinically apparent liver injury with jaundice, but elevations in liver tests led to early discontinuation in at least 2% of subjects. While ponesimod is associated with lymphopenia and long-term therapy is associated with risk for reactivation of herpes simplex and zoster infections, it has not been linked to cases of reactivation of hepatitis B although one such case has been reported with fingolimod. Thus, mild-to-moderate and transient serum enzyme elevations during therapy are common, but clinically apparent liver injury with jaundice due to ponesimod has not been reported, although the clinical experience with its use has been limited.

Likelihood score: E* (suspected but unproven cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which ponesimod might cause liver injury is not known. It is extensively metabolized by liver via multiple enzymes in the cytochrome P450 system, predominantly CYP 3A4, and drug-drug interactions with agents that induce or inhibit these enzymes are likely to occur. Serum enzyme elevations have been frequent with all of the oral S1P receptor modulators, particularly with fingolimod.

Outcome and Management

While chronic therapy with ponesimod can be associated with mild-to-moderate serum aminotransferase elevations, it has not been linked to any cases of clinically apparent liver injury. Because of the frequency of enzyme elevations detected during therapy, the product label for ponesimod recommends obtaining baseline liver tests before initiation of treatment. However, no specific recommendations for monitoring liver tests during treatment have been made. Any ALT or AST elevation associated with symptoms or jaundice should lead to prompt discontinuation of ponesimod. Patients with persistent elevations above 3 times ULN should be assessed for other causes of liver injury and discontinue ponesimod if not other cause is found. There is no known cross sensitivity of the hepatic injury from ponesimod with other agents used to treat multiple sclerosis. Because of the similarity in chemical structure and mechanism of action, there may be cross sensitivity to side effects with fingolimod, siponimod and ozanimod.

Drug Class: Multiple Sclerosis Agents

Other Drugs in the Subclass, S1P Receptor Modulators: Fingolimod, Ozanimod, Siponimod

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ponesimod – Ponvory®

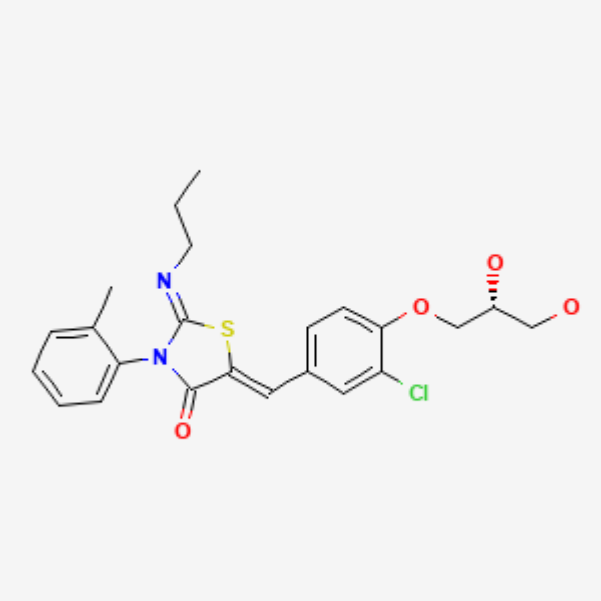
DRUG CLASS

Multiple Sclerosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ponesimod	854107-55-4	C23-H25-Cl-N2-O4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 15 July 2021

Abbreviations: HBV, hepatitis B virus; MRI, magnetic resonance imaging; S1P, sphingosine-1-phosphate.

Zimmerman HJ. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 697-8.

(Expert review of hepatotoxicity published in 1999 before the availability of S1P receptor modulators).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Multi-authored textbook of hepatotoxicity published in 2013 does not discuss the drugs for multiple sclerosis).

Krensky AM, Azzi JR, Hafler DA. Immunotherapy for multiple sclerosis. Immunosuppressants and Tolerogens. In, Brunton LL, Halal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 649-52.

(Textbook of pharmacology and therapeutics).

FDA Medical Review of NDA for Ponesimod: Pages 163-182. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213498Orig1s000MedR.pdf

(FDA website with product labels and medical review of the efficacy and safety of ponesimod mentions that serum aminotransferase elevations above 3 times ULN were not infrequent, analysis of individual instances showed no evidence for clinically apparent liver injury with jaundice).

Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, et al; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362:387–401. PubMed PMID: 20089952.

(Among 1272 patients with relapsing multiple sclerosis treated with fingolimod [0.5 or 1.25 mg daily] or placebo for 24 months, 8.5-12.5% of fingolimod, but only 1.7% of placebo recipients developed ALT elevations above 3 times ULN, and ALT levels fell to normal with or without discontinuation, and serum bilirubin levels did not change).

Olsson T, Boster A, Fernández Ó, Freedman MS, Pozzilli C, Bach D, Berkani O, et al. Oral ponesimod in relapsing-remitting multiple sclerosis: a randomised phase II trial. J Neurol Neurosurg Psychiatry. 2014;85:1198–208. PubMed PMID: 24659797.

(Among 464 adults with relapsing multiple sclerosis treated with ponesimod [10, 20 or 40 mg] or placebo daily for 24 weeks, cumulative numbers of active lesions on MRI between weeks 12 and 24 were lower in ponesimod- [3.4, 1.1 and 14] vs placebo-treated [6.2] patients and annualized relapse rates were lower with the highest dose, while adverse reactions that were more frequent with ponesimod included anxiety, dizziness, insomnia, upper respiratory tract symptoms, peripheral edema and serum ALT elevations [5.6% vs 0.8%] including ALT greater than 3 times ULN [3.8% vs none], but no ALT value was associated with symptoms or jaundice).

Vaclavkova A, Chimenti S, Arenberger P, Holló P, Sator PG, Burcklen M, Stefani M, et al. Oral ponesimod in patients with chronic plaque psoriasis: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet. 2014;384(9959):2036–45. PubMed PMID: 25127208.

(Among 326 patients with plaque psoriasis treated with ponesimod [20 or 40 mg] vs placebo daily for 16 weeks, clinical response rates were higher with active drug [46% and 48%] vs placebo [13%] with higher rates when treatment was continued, while adverse events of ponesimod included dyspnea, dizziness and ALT elevations [14% and 11% vs 3%] and 3 patients discontinued therapy because of ALT elevations, although all were transient and none were associated with symptoms or jaundice).

Subei AM, Cohen JA. Sphingosine 1-phosphate receptor modulators in multiple sclerosis. CNS Drugs. 2015;29:565–75. PubMed PMID: 26239599.

(Review of the function of the S1P receptors [subtypes 1 to 5] and the clinical implications of their differential modulation by different inhibitors).

Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, Rocca MA. Multiple sclerosis. Nat Rev Dis Primers. 2018;4:43. PubMed PMID: 30410033.

(Review of the pathogenesis, clinical features, natural history, management and therapy of multiple sclerosis).

Siponimod (Mayzent)--a new drug for multiple sclerosis. Med Lett Drugs Ther. 2019;61(1571):70–2. PubMed PMID: 31169805.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of siponimod in comparison to other agents used to treat multiple sclerosis; mentions that serum aminotransferase elevations can occur with siponimod therapy and that patients should be tested for liver function tests and have CYP 2C9 genotype testing before starting treatment).

Ozanimod (Zeposia) for multiple sclerosis. Med Lett Drugs Ther. 2020;62(1605):132–4. PubMed PMID: 32970043.

(Concise review of the mechanism of action, clinical efficacy, toxicity and costs of ozanimod shortly after its approval for use in relapsing multiple sclerosis in the US mentions that ozanimod is associated with ALT and AST elevations, and that therapy lowers lymphocyte counts and increases the risk of infections including herpes zoster).

Lu MC, Shih YL, Hsieh TY, Lin JC. Flare of hepatitis B virus after fingolimod treatment for relapsing and remitting multiple sclerosis. J Formos Med Assoc. 2020;119:886–7. PubMed PMID: 31679907.

(Letter describing 41 year old Taiwanese woman with relapsing multiple sclerosis and inactive HBsAg carrier state who developed reactivation of hepatitis B after 35 months of treatment with fingolimod [ALT 385 U/L, HBV DNA 8 $\log_{10}$ IU/mL, bilirubin not given] who responded to tenofovir, with resolution of ALT elevations and decrease of HBV DNA levels to undetectable despite continuation of fingolimod).

Drugs for multiple sclerosis. Med Lett Drugs Ther. 2021;63(1620):42–8. PubMed PMID: 33976089.

(Concise review of the relative clinical efficacy, safety and costs of drugs for relapsing multiple sclerosis including parenteral agents [such as interferon-beta, glatiramer acetate, natalizumab, alemtuzumab, ocrelizumab, ofatumumab, rituximab and mitoxantrone] and the oral agents [such as the S1P receptor modulators, cladribine, fumarates, and teriflunomide], many of which are associated with serum ALT elevations and several have been reported to cause clinically apparent liver injury or reactivation of hepatitis B).

Kappos L, Fox RJ, Burcklen M, Freedman MS, Havrdová EK, Hennessy B, Hohlfeld R, et al. Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis in the active-comparator phase 3 OPTIMUM Study: a randomized clinical trial. JAMA Neurol. 2021;78:558–67. PubMed PMID: 33779698.

(Among 1133 adults with relapsing multiple sclerosis treated with oral ponesimod [20 mg] or teriflunomide [14 mg] once daily for up to 2 years, the annualized relapse rate was lower with ponesimod [0.2 vs 0.3] and overall adverse event rates were similar [89% vs 88%], while ALT elevations were more frequent with ponesimod [any elevation 20% vs 9%, elevation above 3 times ULN in 17% vs 8%, and resulting in discontinuation in 9% vs 6%], yet no patient developed clinically apparent acute liver injury with jaundice).

Markham A. Ponesimod: first approval. Drugs. 2021;81:957–62. PubMed PMID: 33939119.

(Review of the mechanism of action, development, clinical efficacy and safety of ponesimod shortly after its approval in the US in 2021, mentions that serum aminotransferase elevations occurred in 23% of ponesimod recipients in one large preregistration trial).

McGinley MP, Cohen JA. Sphingosine 1-phosphate receptor modulators in multiple sclerosis and other conditions. Lancet 2021 Jun 24: S0140-6736(21)00244-0. Epub ahead of print.

(Review of the function of S1P receptors and the mechanism of action of S1P receptor modulators in affecting lymphocyte tracking out of lymph nodes into the circulation and tissues; fingolimod is a nonspecific modulator affecting all 5 forms of S1P receptors, whereas siponimod and ozanimod act predominantly on S1P receptors 1 and 5 and ponesimod against S1P receptor 1 alone, the activity against S1P receptor-1 accounting for most of the beneficial effects in multiple sclerosis and the restricted specificity perhaps accounting for the lower rate of cardiac, lung and eye adverse events driven mostly by the inhibition of the other S1P receptor subtypes).