SAHARA PUBLIC LIBRARY
Publisher of Scientific Journals

NeuroPharmac Journal
Journal Homepage: https://www.neuropharmac.com

NeuroPharmac

Review

Ponesimod oral therapy for the treatment of relapsing forms of multiple sclerosis in adults and its precautions in cardiovascular disease patients

Mohammed Alrouji*
Department of Medical Laboratories, College of Applied Medical Sciences at Shaqra, Shaqra University, Saudi Arabia

ARTICLE INFO

Article history
Received 15 November 2021,
Revised 20 November 2021,
Accepted 12 December 2021,
Published online
30 December 2021

Keywords
Sphingosine 1-phosphate (S1P) receptor 1 modulator, Ponesimod, multiple sclerosis, cardiovascular disease, Bradyarrhythmia,

ABSTRACT

The ponesimod oral therapy was approved in March 2021 by the United States Food and Drug Administration for relapsing forms multiple sclerosis (MS). Ponesimod is a sphingosine 1-phosphate (S1P) receptor 1 modulator that acts selectively as an anti-inflammatory agent and provides a suitable microenvironment for the function of the other neuroprotective agents. Ponesimod is contraindicated in patients who in the last 6 months, have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure. Also contraindicated in patients who have the presence of Mobitz type II second-degree, third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker. This article briefs the information about dosage, precautions and warnings required in cardiovascular disease patients before initiation of ponesimod oral therapy.

Introduction

Ponesimod is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.[1-2]

Dosage & administration

Before initiation of treatment with ponesimod, assess the following:

Complete Blood Count: Obtain a recent (i.e., within the last 6 months or after discontinuation of prior MS therapy) complete blood count (CBC), including lymphocyte count.

Cardiac Evaluation: Obtain an electrocardiogram (ECG) to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist should be sought and first-dose monitoring is recommended.

Determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction.

Liver Function Tests: Obtain recent (i.e., within the last 6 months) transaminase and bilirubin levels.

Corresponding author at: Department of Medical Laboratories, College of Applied Medical Sciences, Shaqra University, KSA
E-mail address: malrouji@su.edu.sa
https://orcid.org/0000-0001-9645-0572
https://doi.org/10.37881/1.633

Ophthalmic Evaluation: Obtain an evaluation of the fundus, including the macula.
Current or Prior Medications with Immune System Effects: If patients are taking antineoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with ponesimod.
Vaccinations: Test patients for antibodies to varicella-zoster virus (VZV) before initiating ponesimod; VZV vaccination of antibody-negative patients is recommended before commencing treatment with ponesimod. If live attenuated vaccine immunizations are required, administer at least 1 month before initiation of ponesimod.[1-2]

Recommended Dosage

Maintenance Dosage: After dose titration is complete, the recommended maintenance dosage of ponesimod is 20 mg taken orally once daily starting on Day 15. Administer ponesimod orally once daily. Swallow the tablet whole. ponesimod can be taken with or without food.[1-2]
Treatment Initiation: A starter pack must be used for patients initiating treatment with ponesimod. Initiate ponesimod treatment with a 14-day titration; start with one 2 mg tablet orally once daily and progress with the titration schedule as shown in Table 1.[1-2]

Table 1: Dose titration regimen

Titration Day	**Daily Dose**
Day 1 and 2	2 mg
Day 3 and 4	3 mg
Day 5 and 6	4 mg
Day 7	5 mg
Day 8	6 mg
Day 9	7 mg
Day 10	8 mg
Day 11	9 mg
Day 12, 13 and 14	10 mg
Maintenance	**Daily Dose**
Day 15 and thereafter	20 mg

First Dose 4-Hour Monitoring

Administer the first dose of ponesimod in a setting where resources to appropriately manage symptomatic bradycardia are available. Monitor patients for 4 hours after the first dose for signs and symptoms of bradycardia with a minimum of hourly pulse and blood pressure measurements. Obtain an ECG in these patients before dosing and at the end of the 4-hour observation period.
Additional Monitoring After 4-Hour Monitoring: If any of the following abnormalities are present after 4 hours (even in the absence of symptoms), continue monitoring until the abnormality resolves: The heart rate 4 hours post-dose is less than 45 bpm; The heart rate 4 hours post-dose is at the lowest value post-dose, suggesting that the maximum pharmacodynamic effect on the heart may not have occurred; The ECG 4 hours post-dose shows new onset second-degree or higher AV block.
If post-dose symptomatic bradycardia, bradyarrhythmia, or conduction related symptoms occur, or if ECG 4 hours post-dose shows new onset second degree or higher AV block or QTc greater than or equal to 500

msec, initiate appropriate management, begin continuous ECG monitoring, and continue monitoring until the symptoms have resolved if no pharmacological treatment is required. If pharmacological treatment is required, continue monitoring overnight and repeat 4-hour monitoring after the second dose.
Advice from a cardiologist should be sought to determine the most appropriate monitoring strategy (which may include overnight monitoring) during treatment initiation if treatment with ponesimod is considered in patients with some preexisting heart and cerebrovascular conditions; with a prolonged QTc interval before dosing or during the 4-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT-prolonging drugs with a known risk of torsades de pointes; Receiving concurrent therapy with drugs that slow heart rate or AV conduction.[1-2]

Missed dose guideline

Interruption during treatment, especially during titration, is not recommended; however, If fewer than 4 consecutive doses are missed during titration, resume treatment with the first missed titration dose and resume the titration schedule at that dose and titration day. If fewer than 4 consecutive doses are missed during maintenance, resume treatment with the maintenance dosage.
If 4 or more consecutive doses are missed during titration or maintenance, treatment should be reinitiated with Day 1 of the titration regimen (new starter pack). If treatment needs to be reinitiated with Day 1 of the titration regimen (new starter pack), complete first-dose monitoring in patients for whom it is recommended.[1-2]

Contraindications

Ponesimod is contraindicated in patients who in the last 6 months, have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III or IV heart failure. Also contraindicated in patients who have presence of Mobitz type II second-degree, third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker.[1-2]

Bradyarrhythmia and Atrioventricular Conduction Delays

Since initiation of ponesimod treatment results in a transient decrease in heart rate and atrioventricular (AV) conduction delays, and up-titration scheme must be used to reach the maintenance dosage of ponesimod (20 mg).
Study 1 did not include patients who had:
A resting heart rate (HR) less than 50 beats per minute (bpm) on baseline electrocardiogram; Myocardial infarction or unstable ischemic heart disease in the last 6 months; Cardiac failure (New York Heart Association class III-IV) or presence of any severe cardiac disease; Cardiac conduction or rhythm disorders (including sino-atrial heart block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmia, cardiac arrest) either in history or observed at screening; Mobitz Type II second degree AV block or higher-grade AV block observed at screening; QTcF interval greater than 470 ms (females) and greater than 450 ms (males) observed at screening; History of syncope associated with cardiac disorders; Uncontrolled systemic arterial hypertension.[1-2]

Reduction in Heart Rate

Initiation of ponesimod may result in a transient decrease in HR. In Study 1, bradycardia at treatment initiation and sinus bradycardia on ECG (defined as HR less than 50 bpm) occurred in 5.8% of ponesimod-treated patients compared to 1.6% of patients receiving teriflunomide 14 mg. After the first

titration dose of ponesimod, the decrease in heart rate typically begins within an hour and reaches its nadir within 2-4 hours. The heart rate typically recovers to baseline levels 4-5 hours after administration. The mean decrease in heart rate on Day 1 of dosing was 6 bpm. With up-titration after Day 1, the post-dose decrease in heart rate is less pronounced. Bradycardia resolved in all patients in Study 1 without intervention and did not require discontinuation of ponesimod treatment. On Day 1, 3 patients treated with ponesimod had asymptomatic post-dose HR below or equal to 40 bpm; all 3 patients had baseline HRs below 55 bpm.[1-2]

Atrioventricular Conduction Delays

Initiation of ponesimod treatment has been associated with transient atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. In Study 1, the AV conduction delays manifested as first-degree AV block (prolonged PR interval on ECG), which occurred in 3.4% of ponesimod-treated patients and 1.2% of patients receiving teriflunomide 14 mg. The conduction abnormalities typically were transient, asymptomatic, resolved within 24 hours, resolved without intervention, and did not require discontinuation of ponesimod treatment. In Study 1, second and third-degree AV blocks were not reported in patients treated with ponesimod.

If treatment with ponesimod is considered, advice from a cardiologist should be sought for individuals with significant QT prolongation (QTc greater than 500 msec); with atrial flutter/fibrillation or arrhythmia treated with Class Ia or Class III anti-arrhythmic drugs; with unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months before treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months before treatment initiation), or uncontrolled hypertension; with a history of Mobitz Type II second degree AV block or higher-grade AV block, sick- sinus syndrome, or sinoatrial heart block.[1-2]

Treatment Initiation Recommendations

Obtain an ECG in all patients to determine whether preexisting conduction abnormalities are present; In all patients, dose titration is recommended for initiation of ponesimod treatment to help reduce cardiac effects; In patients with sinus bradycardia, first-or second-degree [Mobitz type I] AV block, or a history of myocardial infarction or heart failure with onset more than 6 months before initiation, first-dose monitoring is recommended; Ponesimod is not recommended in patients with a history of cardiac arrest, cerebrovascular disease (e.g., TIA, stroke occurring more than 6 months before treatment initiation), uncontrolled hypertension, or severe untreated sleep apnea, since significant bradycardia may be poorly tolerated in these patients. If treatment is considered, advice from a cardiologist should be sought before initiation of treatment to determine the most appropriate monitoring strategy; Use of ponesimod in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought before initiation of treatment to determine the most appropriate monitoring; Experience with ponesimod is limited in patients receiving concurrent therapy with drugs that decrease heart rate (e.g., beta-blockers, non-dihydropyridine calcium channel blockers - diltiazem and verapamil, and other drugs that may decrease heart rate such as digoxin). Concomitant use of these drugs during ponesimod initiation may be associated with severe bradycardia and heart block. If treatment is considered, advice from a cardiologist should be sought before initiation of treatment to determine the most appropriate monitoring.[1-2]

For patients receiving a stable dose of a beta-blocker, the resting heart rate should be considered before introducing ponesimod treatment. If the resting heart rate is greater than 55 bpm under chronic beta-blocker treatment, ponesimod can be introduced. If the resting heart rate is less than or equal to 55 bpm,

beta-blocker treatment should be interrupted until the baseline heart rate is greater than 55bpm. Treatment with ponesimod can then be initiated and treatment with a beta-blocker can be reinitiated after ponesimod has been up-titrated to the target maintenance dosage.[1-2]

For patients taking other drugs that decrease heart rate, treatment with ponesimod should generally not be initiated without consultation from a cardiologist because of the potential additive effect on heart rate.[1-2]

Conflicts of Interest

The author declares that there are no conflicts of interest relevant to this article.

References

1. US Food and Drug Administration. FDA-approved drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=213498. Accessed 03 November 2021.
2. Medscape. Ponesimod. https://reference.medscape.com/drug/ponvory-ponesimod-4000139. Accessed 03 November 2021.

Cite this article

Alrouji M. Ponesimod oral therapy for the treatment of relapsing forms of multiple sclerosis in adults and its precautions in cardiovascular disease patients. NeuroPharmac J. 2021; 6(3): 248-252. DOI: 10.37881/1.633