PONVORY®▼(ponesimod)

PRESCRIBER'S CHECKLIST

Important points to remember before, during, and after treatment

Adverse events should be reported. ▼ This medicinal product is subject to additional monitoring and it is therefore important to report any suspected adverse events related to this medicinal product.

Healthcare professionals are asked to report suspected adverse events via: HPRA Pharmacovigilance Website: www.hpra.ie. Adverse events should also be reported to Juvisé Pharmaceuticals on +33 (0)4 26 29 40 00 or email pv@juvise.com

JUVISE® pharmaceuticals

Approved 12/2024

Introduction to the Prescriber's checklist

This guide provides essential information on the most important identified and potential risks associated with PONVORY® and the activities required to minimise these risks (as defined within the PONVORY® Risk Minimisation Plan).

Reading this material is essential to ensure the safe and effective use of PONVORY® and appropriately manage important selected risks.

This checklist does not contain all of the information related to the adverse drug reaction profile of PONVORY®, or the relevant prescribing information. The prescriber's checklist should therefore be read in conjunction with the PONVORY® Summary of Product Characteristics (SmPC). For more detailed guidance on PONVORY®, please refer to the SmPC at: www.medicines.ie.

A patient/caregiver guide and a pregnancy-specific patient reminder card have also been developed as part of the risk minimisation plan and should be used to inform your discussion with the patient.

Therapeutic indication:

PONVORY® is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features.

Contraindications:

PONVORY® is contraindicated in patients who have:

- Hypersensitivity to the active substance or to any of the excipients
- An immunodeficient state
- Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischaemic attack (TIA), decompensated heart failure requiring hospitalisation, or New York Heart Association (NYHA) Class III or IV heart failure
- Presence of Mobitz Type II second-degree atrioventricular (AV) block, third-degree AV block, or sick sinus syndrome, unless the patient has a functioning pacemaker
- Severe active infections or active chronic infections
- Active malignancies
- Moderate or severe hepatic impairment (Child-Pugh Class B and C respectively)
- Become pregnant and in women of childbearing potential not using effective contraception

Not recommended:

- Patients with unstable ischemic heart disease, cardiac decompensated failure occurring more than 6 months prior to treatment initiation, history of cardiac arrest, cerebrovascular disease (TIA, stroke occurring more than 6 months prior to treatment initiation), and uncontrolled hypertension, since significant bradycardia may be poorly tolerated in these patients, treatment is not recommended
- Ponvory has not been studied in children and adolescents, therefore it is not recommended for use in children and adolescents aged less than 18 years

Recommended steps to managing patients on PONVORY® (ponisemod)

This checklist is intended to assist in the management of patients being treated with PONVORY®. Important points to remember before, during, and after treatment are included.

Patient's name: _____
Date of birth: _____
Consultant: _____
Hospital Number: _____

PRIOR TO INITIATING TREATMENT

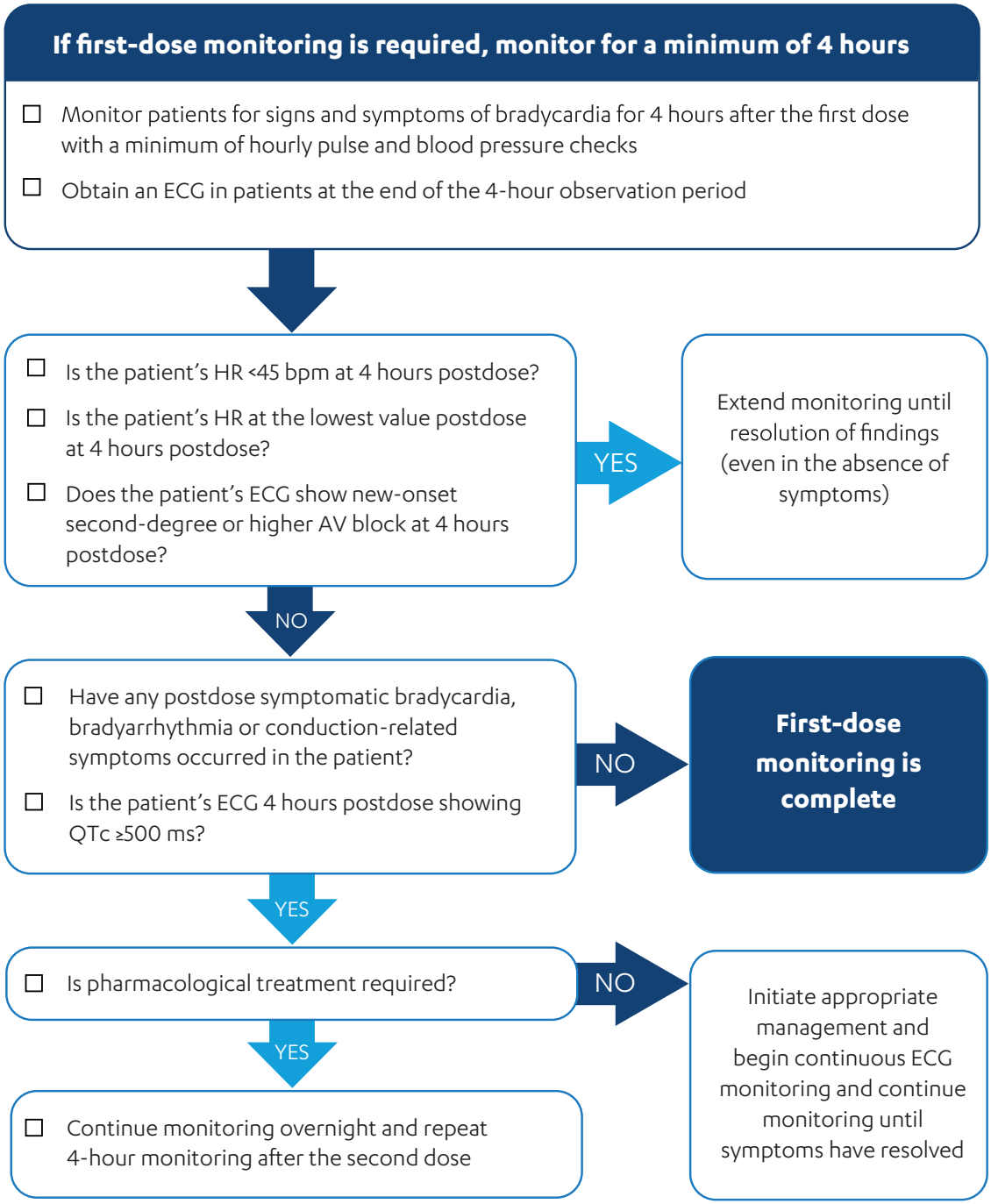
	Mandatory requirements before initiating treatment
☐	Perform an electrocardiogram (ECG) to determine whether any pre-existing cardiac abnormalities are present First-dose monitoring is recommended for patients with certain pre-existing cardiac conditions: • Sinus bradycardia (HR <55 beats per minute [bpm]) • First- or second-degree (Mobitz Type I) AV block; or • A history of myocardial infarction or heart failure occurring more than 6 months prior to treatment
☐	Consult a cardiologist before initiation of PONVORY® in the following patients to determine the overall benefit-risk and the most appropriate monitoring strategy: • Patients with significant QT prolongation (QTc >500 ms) or who are already being treated with QT-prolonging medicinal products with known arrhythmogenic properties (risk of torsades de pointes) • Patients with atrial flutter/fibrillation or arrhythmias treated with Class Ia (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products • Treatment is not recommended in patients with the following conditions as they may not tolerate significant bradycardia: unstable ischaemic heart disease; previous cardiac arrest; decompensated heart failure or cardiovascular disease (stroke or TIA) occurring more than 6 months before starting PONVORY®; or uncontrolled hypertension. • Patients with a history of Mobitz Type II second-degree AV block or higher-grade AV block, sick-sinus syndrome, or sinoatrial heart block • Patients with a history of recurrent syncope or symptomatic bradycardia • Patients receiving concurrent therapy with drugs that decrease heart rate (HR) (e.g. beta blockers, non-dihydropyridine calcium channel blockers [diltiazem and verapamil] and other drugs that may decrease HR, such as digoxin); consider the need to switch to non-HR-lowering medicinal products Concomitant use of these medicinal products during PONVORY® initiation may be associated with severe bradycardia and heart block
☐	Review results of a recent (obtained within 6-months prior to treatment initiation or after discontinuation of prior multiple sclerosis therapy) full blood count (FBC) with differential white count (including absolute lymphocyte count)
☐	Review results of a recent (within 6 months prior to treatment initiation) liver function test for transaminase and bilirubin levels

☐	Obtain ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation. PONVORY® should not be initiated in patients with macular oedema until resolution
☐	Instruct patients to report changes in vision
☐	A pregnancy test is recommended before treatment in all women of childbearing potential
☐	Counsel women of childbearing potential on the potential risk of teratogenicity and the need for effective contraception during treatment with PONVORY® and for at least 1 week following treatment discontinuation
☐	Counsel women of childbearing potential to discontinue treatment with PONVORY® at least 1 week before attempting to conceive • Explain to the patient that their disease activity may return when treatment with PONVORY® is discontinued due to pregnancy or attempting to conceive
☐	Instruct women receiving PONVORY® that they should not breastfeed
☐	Perform a varicella zoster virus (VZV) antibody test in patients without a confirmed history of varicella or adequate vaccination against VZV • A full course of vaccination for antibody-negative patients with VZV vaccine is recommended prior to commencing treatment with ponesimod • VZV vaccination is only indicated if the VZV antibody test is negative • The full course of VZV vaccination should be completed at least 4 weeks before starting PONVORY®
☐	Initiation of treatment with PONVORY® should be delayed in patients with severe active infection until resolution
☐	Review current or prior medications. If patients are taking antineoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these medicinal products, consider possible unintended additive effects on the immune system before treatment initiation

ROUTINE FIRST-DOSE MONITORING

Cardiology advice on monitoring should be followed if necessary.

If first-dose monitoring for patients with pre-existing cardiac conditions is required, follow the steps outlined below:



bpm, beats per minute; ECG, electrocardiogram; HR, heart rate; QTc, Heart-rate-corrected QT interval.

☐ The patient does not have applicable pre-existing cardiac conditions and therefore first-dose monitoring is not required

TREATMENT INITIATION (INCLUDING RE-INITIATION CRITERIA)

Dose escalation at treatment initiation

Initiate treatment with the 14-day treatment initiation pack. Start treatment on Day 1 with one 2 mg tablet orally once daily and progress with the 14-day titration schedule outlined in the following diagram:

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

- After dose titration is complete, the recommended maintenance dose of PONVORY® is one 20 mg tablet taken orally once daily.

Re-initiation of PONVORY® therapy following treatment interruption during dose titration or maintenance period

- **If fewer than 4 consecutive doses are missed**, resume treatment with the first missed dose
- **If 4 or more consecutive doses are missed**, re-initiate treatment with Day 1 (2 mg) of the titration regimen (using a new treatment initiation pack)
    - The same first-dose monitoring as for treatment initiation is recommended when 4 or more consecutive doses of PONVORY® are missed during the titration or maintenance periods in patients with pre-existing cardiac conditions

DURING TREATMENT

Lymphocyte count

- ☐ Assess FBC periodically during PONVORY® treatment
  - Absolute lymphocyte counts <0.2×10^9/L, if confirmed, should lead to interruption of PONVORY® therapy until the level reaches >0.8×10^9/L, after which re-initiation of PONVORY® can be considered

Considerations relating to immunosuppressive effect

- ☐ Carefully monitor patients, especially those with concurrent conditions or known risk factors, such as previous immunosuppressive therapy. Discontinuation of treatment in patients at increased risk of infections or malignancies should be considered on a case-by-case basis
- ☐ Consider suspension of treatment during serious infection
- ☐ Carefully consider the risk of synergistic immunosuppressive effects when co-prescribing antineoplastic, immunomodulatory or immunosuppressive therapies
- ☐ Monitor patients for skin malignancies:
  - Suspension of treatment should be considered in those with serious infections
  - Caution patients against exposure to UV light and sunlight without protection
  - Ensure patients are not receiving concomitant phototherapy with ultraviolet B (UVB) radiation or psoralen and ultraviolet A photochemotherapy (PUVA)
  - Patients with pre-existing skin disorders and patients with new or changing skin lesions should be referred to a dermatologist to for advice on management
- ☐ Vigilance for signs and symptoms of infection is recommended. Instruct patients to report signs and symptoms of infections immediately to their prescriber during treatment, and for up to 1 week after the last dose of PONVORY®
  - Cases of fatal cryptococcal meningitis (CM) and disseminated cryptococcal infections have been reported in patients treated with other sphingosine-1-phosphate (S1P) receptor modulators
    - Suspend treatment with PONVORY® if CM is suspected until cryptococcal infection has been excluded
    - Initiate appropriate treatment if CM is diagnosed
  - Cases of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain caused by the John Cunningham polyoma virus, have been reported in patients treated with another S1P receptor modulator and other MS therapies. Physicians should be vigilant for clinical signs and symptoms or MRI findings suggestive of PML
    - Suspend treatment with PONVORY® if PML is suspected until PML has been excluded
    - Discontinue treatment with PONVORY® if PML is confirmed
- ☐ Use of live attenuated vaccines may carry a risk of infection and should therefore be avoided during treatment and for up to 1 week after its discontinuation
  - If the use of live attenuated vaccines during treatment with PONVORY® is required, treatment should be paused 1 week prior and for 4 weeks after a planned vaccination

Ophthalmic evaluation	
☐	Obtain an ophthalmic evaluation of the fundus, including the macula, at any time if a patient reports any change in vision while on PONVORY® therapy
☐	Instruct patients to report changes in vision
☐	Evaluate patients who present with visual symptoms of macular oedema • Discontinue treatment with PONVORY® if macular oedema is confirmed • Consider the potential benefits and risks of PONVORY® after resolution of macular oedema before treatment re-initiation
☐	Conduct regular follow-up examinations of the fundus, including the macula, in patients with a history of uveitis or diabetes mellitus
For women of childbearing potential	
☐	Repeat pregnancy tests at suitable intervals during treatment
☐	Before initiation and during treatment with PONVORY®, counsel women of childbearing potential on the possibility of serious risk to the foetus during treatment with PONVORY®, using the pregnancy-specific patient reminder card
☐	Instruct women of childbearing potential to use effective contraception during treatment with PONVORY® and for at least 1 week following treatment discontinuation
☐	Counsel women of childbearing potential to discontinue treatment with PONVORY® at least 1 week before attempting to conceive • Explain to the patient that their disease activity may return when treatment with PONVORY® is discontinued due to pregnancy or attempting to conceive
☐	Immediately discontinue treatment with PONVORY® if a woman becomes pregnant during treatment. Provide medical advice regarding the risk of harmful effects to the foetus associated with PONVORY® treatment and ensure follow-up examinations are performed
☐	Instruct women receiving PONVORY® that they should not breastfeed
☐	If a pregnancy occurs during treatment with PONVORY®, regardless of it being associated with an adverse event or not, please report it to Juvisé Pharmaceuticals on +33 (0)4 26 29 40 00 or at pv@juvise.com. • Juvisé Pharmaceuticals has developed a **P**regnancy **O**utcomes **E**nhanced **M**onitoring (POEM) programme designed to collect information about pregnancy in patients exposed to PONVORY® immediately before or during pregnancy and on infant outcomes 12 months post-delivery • Physicians are encouraged to enrol pregnant patients in the POEM programme by contacting Juvisé Pharmaceuticals on +33 (0)4 26 29 40 00 or at pv@juvise.com. • For more information, refer to the pregnancy reminder card for women of childbearing potential
☐	A pregnancy test is not applicable to this patient
☐	Counselling on pregnancy precautions is not applicable to this patient
Considerations relating to liver function	
☐	Monitor patients who develop symptoms suggestive of hepatic dysfunction during treatment with PONVORY® for hepatotoxicity
☐	Discontinue treatment if significant liver injury is confirmed (e.g. alanine aminotransferase [ALT] exceeds 3× upper limit of normal [ULN] and total bilirubin exceeds 2×ULN)

Respiratory considerations	
☐	Perform spirometry evaluation of respiratory function during treatment with PONVORY® if clinically indicated
Blood pressure considerations	
☐	Regularly monitor blood pressure during treatment with PONVORY®
Neurological considerations	
☐	Seizures have been reported in patients treated with PONVORY®. Physicians should be vigilant for seizures, especially in patients with a pre-existing history of seizures or a family history of epilepsy
☐	Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving an S1P receptor modulator • Promptly schedule a complete physical and neurological examination if a PONVORY®-treated patient develops unexpected neurological or psychiatric signs or symptoms, signs or symptoms suggestive of increased intracranial pressure, or accelerated neurological deterioration and an MRI should be considered • Discontinue treatment with PONVORY® if PRES is suspected • Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae
Additional considerations	
☐	Provide all patients with the patient/caregiver guide
☐	Provide all patients with the pregnancy-specific patient reminder card if appropriate

AFTER TREATMENT DISCONTINUATION

Peripheral blood lymphocyte counts	
☐	Vigilance for signs and symptoms of infection should be continued for 1-2 weeks after PONVORY® is discontinued
Considerations relating to immunosuppressive effect	
☐	Exercise caution when co-administering anti-neoplastic, immune-modulating, or immunosuppressive therapies due to the risk of additive immune system effects. Caution should be applied during concomitant administration and up to 1 week after the last dose of PONVORY®
Vaccines	
☐	Use of live attenuated vaccines may carry a risk of infection and should therefore be avoided during treatment and for up to 1 week after its discontinuation • Counsel patients on the potential reduction in vaccine effectiveness and therefore avoid vaccination during treatment with PONVORY® and up to 1 week after its discontinuation • Treatment should not be resumed until 4 weeks after a planned vaccination if the use of live attenuated vaccine immunisation is required
Ophthalmic evaluation	
☐	Consider the potential benefits and risks of PONVORY® after resolution of macular oedema before treatment re-initiation

For women of childbearing potential	
☐	Counsel women of childbearing potential on the potential for serious risk to the foetus and the need for effective contraception during, and for 1 week after, stopping PONVORY® as it takes approximately 1 week to eliminate PONVORY® from the body • Consider the possible return of disease activity when stopping PONVORY® therapy for a planned pregnancy
☐	Provide medical advice regarding the risk of harmful effects to the foetus associated with PONVORY® treatment and ensure follow-up examinations are performed after discontinuation of treatment with PONVORY® if a woman becomes pregnant during treatment
Cardiac considerations	
☐	When treatment is interrupted if the resting heart rate (HR) is less than or equal to 55 bpm in patients receiving a stable dose of a beta-blocker, you can consider re-initiation with PONVORY® when: • The baseline HR is greater than 55 bpm
Additional considerations	
☐	Observe patients for a severe exacerbation or return of high disease activity upon PONVORY® discontinuation and appropriate treatment should be instituted, as required

AR-PI-00725-1
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Approved 12/2024

Reference: PONVORY® (ponesimod) Summary of Product Characteristics. Available from: www.medicines.ie