Protocol

Ponesimod (Ponvory®) treatment of relapsing-remitting multiple sclerosis (MS)

1 Scope

Treatment of patients with a diagnosis of multiple sclerosis by the MS team at Cambridge University Hospitals NHS Foundation Trust (CUH).

2 Purpose

To ensure the safe administration of ponesimod (Ponvory®).

3 Introduction

Ponesimod is indicated for treatment of people with active relapsing-remitting multiple sclerosis with active disease defined by clinical or imaging features. For reference, in the OPTIMUM study this was defined as 1 relapse in 1 year, 2 relapses in the last 2 years or a Gd-enhancing lesion.

The use of Ponesimod in women of child bearing potential should be carefully considered due the risks of teratogenicity (see section 6.1).

4 Undertaken by (staff groups)

Medical staff and nursing staff who are competent to carry out the procedure.

5 Clinical equipment list

12 lead ECG (pre-treatment screening)
Vital signs monitor (for pre- and post- first dose if certain pre-existing cardiac conditions (see section 6.2).

6 Treatment

6.1 Eligibility and screening

Patients will have been assessed as eligible for treatment by a consultant neurologist in the disease modifying therapy clinic. NICE technology appraisal guidance Ponesimod for treating relapsing-remitting multiple sclerosis [TA767] (2022) will be followed when assessing eligibility. Risks and benefits will have

been discussed. Medications and co-morbidities will have been documented on Epic.

Pre-treatment screening will have occurred in the outpatient clinic setting:

- 12 lead electrocardiogram (ECG): if any of the following pre-existing cardiac conditions are present, first-dose monitoring is recommended:
  - 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
- Referral to cardiologist for risk/ benefit assessment and monitoring strategy if:
  - 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
  - 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
- Screening blood tests are sent as outlined in the Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.
- In patients with a history of diabetes or uveitis, obtain evaluation of the fundus, including the macula, by ophthalmology **prior** to treatment initiation. PONVORY® should not be initiated in patients with macular oedema until resolution
- A pregnancy test is recommended before treatment in all women of childbearing potential
- Pregnancy (and the risk of teratogenicity), breast feeding (which is not recommended) and importance of contraception whilst on treatment and for 1 week after discontinuation discussed and documented
  - Explain to patient that their disease activity may return when treatment with PONVORY is discontinued due to pregnancy or attempting to conceive
- Vaccine advice given as per Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.

    - In particular, varicella zoster virus antibody test must be performed prior to initiation:
        - A full course of vaccination for antibody-negative patients with VZV vaccine is recommended prior to commencing treatment with ponesimod
        - 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 immunomodulating 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
- Baseline expanded disability status scale (EDSS)
- Neurologist asks patient if any concerning **skin lesions**, reviews lesions and refers patient to dermatology if necessary.

When the patient decides to start ponesimod the MS nurse:

- Sends a standard letter recording the consent discussions to the patient with copy to GP (using smart text .PONESIMODCONSENT). This is sent prior to the admission for the first dose.
- Ensures Blueteq form is completed and patient added to database.
- MS nurse explains the delivery service.
- For patients with diabetes or a history of uveitis, MS nurse explains to patient plan for Ophthalmology review and pupil dilatation prior to treatment initiation and 3 months after starting. MS nurse alerts ophthalmology (via Mr Newman's secretary) to expect the patient for screening and for a check at 3 months.
- MS nurse instructs patient to report any changes in vision whilst taking Ponesimod to them immediately. If this occurs, the MS nurses are to arrange urgent Ophthalmology review (including examination of fundus (including macula))
    - If macular oedema is found, PONVORY must be discontinued immediately. Once resolved, the benefits and risks should be weighed-up before considering re-commencement.

6.2 Contraindications and cautions

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

Ponvory is not recommended in:

- 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

6.3 Dosage

The dose of ponesimod is titrated up over a 2 week period as below:

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
Day 15 onwards maintenance	20 mg

6.3.1 Side effects

Ponesimod is normally well tolerated however the following side effects can occur.

Very common and common

- Can increase the risk of infections e.g. nasopharyngitis, upper respiratory tract infection, urinary tract infections, bronchitis, influenza, rhinitis, sinusitis, herpes zoster, pneumonia. **During the COVID-19 pandemic the ABN Guidance On The Use Of Disease-Modifying Therapies In Multiple Sclerosis In Response To The COVID19 Pandemic will be followed** (Date: August 2021, published 26/10/21).

- Lowering in WBC. NB: Lymphopenia (to be expected – see follow up and management)
- Depression, insomnia and anxiety
- Dizziness including vertigo
- Fatigue
- Migraine
- Hypoasthesia
- Blurred vision and macular oedema – see follow-up and monitoring
- Hypertension
- Cough and dyspnoea
- Indigestion
- Back pain, pain in extremity, ligament sprain and arthralgia
- Fever, peripheral oedema, chest discomfort
- Elevated liver function tests
- Hypercholesterolaemia
- CRP increase

Uncommon

- Bradycardia and AV block
    - Sinus bradycardia occurred in 6% of those on ponesimod in the OPTIMUM study. These were generally asymptomatic, resolved without intervention and did not require discontinuation. 3% of patients had first-degree AV block, which were generally asymptomatic, resolved without intervention and did not require discontinuation.
- Dry mouth
- Join swelling
- Hyperkalaemia

6.4 Switching to ponesimod from other therapies

When switching disease modifying treatment the following breaks in treatment are required prior to commencing ponesimod:

- **Beta interferon or glatiramer acetate**: no wash out period is required prior to starting ponesimod.
- **Natalizumab**: there must be no exposure to natalizumab for one to two months prior to ponesimod.

6.5 Prescription and booking first dose

- For those needing monitoring (see Section 6.6), MS nurse arranges date for day admission and informs Outpatient pharmacy of the date supply will be required. Asks for Blueteq form to be completed by MS secretary.
- MS nurse asks consultant neurologist to prescribe outpatient ponesimod on Epic as per following:

- Consultant neurologist prescribes titration and maintenance orders on Epic routed to Outpatient Pharmacy with 0 refills as follows:
    - Epic button top left of screen -> orders only -> enter patient hospital number -> select patient
    - Orders only tab -> 'problem list' section -> ensure relapsing remitting multiple sclerosis entered -> add problem to visit diagnosis by clicking on the icon of a piece of paper with an arrow (next to resolve button)
    - In orders only tab go to 'medication and orders' section -> new order box, put cursor in box and press enter -> brings up preference list browser -> DMTs (OP meds) -> tick box for ponesimod titration order -> select
    - Automatically brings up prescription 'Ponesimod titration schedule'.
    - Automatically brings up prescription 'Ponesimod maintenance take one capsule once daily for 28 days'
    - Click on this to open and check details are correct as follows:
        - Ponesimod 20mg daily
        - Intended use multiple sclerosis as per NHSE policy
        - Dose 20mg, route oral
        - Frequency daily
        - Duration 28 days
        - **Enter start date**
        - Marked long term
        - Patient instruction 'Take one capsule once daily for 28 days'
        - Dispense 28 capsule, refill 0
            - Class: Outpatient Pharmacy
            - Accept
            - Sign prescription
            - Then sign visit
    - MS secretary should be informed of the new starter and prepare the homecare prescription for signing and supply to pharmacy neurology team for screening.

6.6 First dose administration

First-dose monitoring is only required in 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

For these patients:

- MS nurse collects ponesimod titration and maintenance doses from Outpatient Pharmacy (preferably on the day before the patient is due for admission).
- Patient attends the infusion unit in the morning, infusion nurse does the following:
    - Asks female patients if there is a possibility of pregnancy and does a pregnancy test in all women of childbearing potential.
    - Records baseline pulse and blood pressure (BP). If pulse rate is below 45 beats per minute consult the neurology doctor prior to administration.
- If heart rate and BP satisfactory, neurology SpR prescribes on the Epic inpatient chart a single dose of ponesimod [as per titration plan above]
- First-dose monitoring involves
    - Hourly pulse and BP recorded for four hours after the first dose
    - 12 lead ECG shown to the neurology SpR after 4 hours
- Additional monitoring after 4-hours is recommended if any of the following abnormalities are present (even in the absence of symptoms), continue monitoring until the abnormality resolves:
        - HR 4 hours post-dose is less than 45 bpm
        - HR 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, brady-arrhythmia, 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. In this setting ponesimod will be discontinued. The titration and maintenance drugs should be returned to Outpatient pharmacy within 48 hours. Where a dose has been used from the titration pack, it will be destroyed. The maintenance pack will be returned to stock.
- Follow Trust protocol if an allergic reaction or anaphylaxis occur
- Supply of ponesimod for 14 day titration and 28 day maintenance given to patient to take home.
- MS nurse sends discharge letter to GP using smartphrase. PONESIMODFIRSTDOSE and checks the plan is in place for MS nurse follow up at month 3, where patients will be explicitly asked about their vision.

7 Follow up and monitoring

7.1 Outpatient appointments and safety monitoring

Patients are to be monitored after treatment, in a clinic setting, by consultant neurologist and team with special interest in MS. Clinic follow-up should be tailored to the needs of the patient, below is the minimum clinic review schedule:

- MS nurse clinic review at month 3, explicitly asking whether there has been any deterioration in vision. If so – or if the patient has a history of diabetes or uveitis (irrespective of any visual deterioration whilst on ponesimod) – the MS nurse will book urgent ophthalmology review to include fundoscopy to exclude macular oedema.
- Ophthalmology department should have entered ophthalmology result onto Epic within two weeks, MS nurse to check. Responsibility for Ponesimod ophthalmology review lies with the nurse doing the month 3 appointment, if despite the MS nurse's best efforts the ophthalmology outcome is not documented on EPIC it should be escalated to the doctor.
- Year 1 MS nurse reviews (asks about skin lesions and visual deterioration)
- Year 2 Dr (reviews skin lesions + EDSS)
- Then alternate nurse/Dr annually if stable
- A baseline MRI scan within 3 months of starting ponesimod should be order by the doctor.

Any pregnancies on ponesimod will be reported to Janssen-Cilag on (01494) 567447 or at dsafety@its.jnj.com

To date there have been a small number of cases of PML in patients treated with another S1P receptor modulator and other MS therapies. If PML is suspected, MRI brain should be performed immediately and treatment with ponesimod should be suspended until PML has been excluded.

7.2 Blood Monitoring

- Month 1 and 3 (FBC, LFT), then if LFT normal 6 monthly FBC and LFT.
- After month 12 if bloods stable can reduce to annual FBC and LFT during the COVID19 pandemic in line with the ABN Guidelines Oct 2021.
- Suspend ponesimod if the lymphocyte count is $0.1x10^9$/l or less.
- If the lymphocyte count is > $0.1x10^9$/l **but** < $0.2x10^9$/l confirm the result on a repeat of the FBC.
- If confirmed, monitor the FBC and patient closely for signs of infection (including PML) and consider suspending ponesimod.
- Suspend ponesimod if serum hepatic transaminases 5x upper limit of normal. If there is doubt that ponesimod was the cause and LFT recover can restart ponesimod and monitor closely.
- If no symptoms of liver injury and ALT greater than 3x ULN but less than 5xULN, and bilirubin normal, continue ponesimod and monitor more frequently.

7.3 Treatment breaks/ missed doses

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

8 Stopping criteria

- Development of secondary progression with sustained loss of ambulation for greater than six months
- No reduction in frequency or severity of relapses compared with pre-treatment following at least three months of ponesimod
- Unacceptable adverse effects
- Allergic reaction to ponesimod
- Macular oedema
- Unresolved brady-arrhythmia
- Pregnancy and breast feeding
- Confirmed reduction in lymphocyte count to less than $0.1x10^9$/l (consider stopping if lymphocyte count is greater than $0.1x10^9$/l but less than $0.2x10^9$/l)
- Recurrent infections requiring medical treatment or single serious infection
- Elevation in serum levels of hepatic transaminases. 5x upper limit of normal (can retry when normalised)
- Persistent failure to keep booked appointments
- Patients need to continue to use effective contraception and report signs or symptoms of infection for two months after treatment is stopped

9 Monitoring compliance with and the effectiveness of this document

(a) Process for monitoring compliance and effectiveness

- Patients will be assessed as a minimum every 12 months for continued eligibility for treatment by consultant neurologist or MS specialist nurse
- Patients will agree before starting treatment: to comply with treatment protocol, keep appointments and contact relevant healthcare professionals in the event of changes in their underlying MS condition or suspected side effects

- Ongoing maintenance of database of patients offered treatment, undergoing treatment and stopping treatment, including reason for stopping treatment, will be kept by the MS specialist nurse to audit against NICE guidelines
- The MS team will be vigilant for post marketing safety data.

(b) Standards/ key performance indicators

- The audit department will request evidence of compliance with NICE guideline.
- Internal checks on safety, compliance and efficacy will be undertaken by MS team.

10 References

National Institute for Health and Care Excellence. (2022). Ponesimod for treating relapsing–remitting multiple sclerosis Technology Appraisal TA767. https://www.nice.org.uk/guidance/ta767

Olsson T, Boster A, Fernández Ó, et al. Oral ponesimod in relapsing-remitting multiple sclerosis: a randomised phase II trial. *J Neurol Neurosurg Psychiatry*. 2014;85(11):1198-1208.

Kappos L, Fox RJ, Burcklen M, 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(5):558–567.

Ponvory Summary of product characteristics (2022). Retrieved from: https://www.ema.europa.eu/en/documents/product-information/ponvory-epar-product-information_en.pdf

ABN Guidance On The Use Of Disease-Modifying Therapies In Multiple Sclerosis In Response To The COVID19 Pandemic (Date: August 2021, published 26/10/21). https://cdn.ymaws.com/www.theabn.org/resource/collection/6750BAE6-4CBC-4DDB-A684-116E03BFE634/21.10.26_ABN_Guidance_on_DMTs_for_MS_and_COVID-19.pdf

Treatment Algorithm for Multiple Sclerosis Disease-modifying Therapies NHS England Reference: 170079ALG Date Published: 4 September 2018 Gateway reference: 07603 https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2018/09/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-modifying-Therapies.pdf

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