Protocol

Siponimod (Mayzent®) treatment of secondary progressive multiple sclerosis (SPMS)

1 Scope

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

2 Purpose

To ensure the safe administration of siponimod (Mayzent®).

3 Introduction

Siponimod is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.

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 and pre and post first dose) **may** be needed
- vital signs monitor

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. See NICE technology appraisal Siponimod for treating secondary progressive multiple sclerosis Technology appraisal guidance [TA656]. Risks and benefits will have been discussed. Medications and co-morbidities will have been documented on Epic.

Pre-treatment screening

The following must be provided by the MS team:

- Doctor review of any skin lesions and referral patient to dermatology if necessary.
- Vaccine advice given as per Multiple sclerosis (MS) disease modifying therapy (DMT) initiation and monitoring SOP.
- Baseline expanded disability status scale (EDSS).
- Baseline MRI brain scan ordered (should be done within three months of starting treatment).
- Pregnancy, breast-feeding and importance of contraception whilst on treatment discussed and documented.
- If history of diabetes or uveitis, the patient is referred for baseline ophthalmic assessment to exclude macular oedema.
- If history of cardiovascular or cerebrovascular disease patient will have been referred to cardiologist for risk/ benefit assessment.
- Review of medications prior to the first dose: if the patient is on a beta-blocker and resting HR is less than 50 bpm, consider pausing beta-blocker until heart rate has risen to above 50 bpm.
- Counsel patients to report visual disturbances at any time.

The following screening tests may occur in an NHS outpatient setting, or provided by a home healthcare service:

- Screening blood tests are sent as outlined in the Multiple sclerosis (MS) disease modifying therapy (DMT) initiation and monitoring SOP.
- 12-lead electrocardiogram (ECG).
- Genotyping (as below).

When the patient decides to start siponimod, the MS nurse or doctor:

- Sends a standard letter recording the consent discussions to the patient with copy to GP (using smart text .SIPONIMODCONSENT). 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 and monitoring service.
- MS nurse explains to patient plan for ophthalmology review and pupil dilatation at month 3.
- MS nurse requests month 3 MS nurse appointment and refers to ophthalmology for screening using Epic.

6.2 Genotyping at screening

Before initiation of treatment, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. This influences the dose of siponimod to be used (see below).

6.3 Contraindications and cautions

- First dose precautions [see below] should be taken for those with sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block, history of myocardial infarction, or history of heart failure (patients with NYHA class I and II).
- Hypersensitivity to the active substance, or to peanut, soya or any of the excipients.
- Immunodeficiency syndrome.
- History of progressive multifocal leukoencephalopathy or cryptococcal meningitis.
- Active malignancies.
- Severe liver impairment (Child-Pugh class C).
- Patients who in the previous six months had a myocardial infarction (MI), unstable angina pectoris, stroke/ transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure.
- Patients with a history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a pacemaker.
- Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser).
- During pregnancy and in women of childbearing potential not using effective contraception.
- Due to the risk of serious cardiac rhythm disturbances or significant bradycardia, **siponimod should not be used** in patients with a history of symptomatic bradycardia or recurrent syncope, uncontrolled hypertension, or severe untreated sleep apnoea.

6.4 Dosage

The maintenance dose of siponimod depends on genotype:

CYP2C9 genotype	Prevalence	Maintenance dose
9*3*3	0.4%	siponimod should not be used
9*2*3 or *1*3	15%	1 mg taken once daily
All other genotypes	84%	2 mg taken once daily

There is a dose titration regime over a few days:

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Maintenance dose
0.25mg	0.25mg	0.5mg	0.75mg	1.25mg	2mg	2mg
0.25mg	0.25mg	0.5mg	0.75mg	1.25mg	1mg	1mg

During the first six days of treatment, if a titration dose is missed on one day treatment needs to be re-initiated with a new titration pack.

If maintenance treatment is interrupted for four or more consecutive daily doses, siponimod needs to be re-initiated with a new titration pack.

6.5 Side effects

Siponimod is generally well tolerated but these may occur:

Very common and common

- Can increase the risk of infections eg influenza, sinusitis, herpes zoster, bronchitis.
- Basal cell carcinoma and melanocytic naevus – see follow up and management.
- Lowering in WBC. NB: lymphopenia (to be expected) – see follow up and management.
- Elevated liver function tests.
- Depression.
- Headache.
- Dizziness.
- Seizure.
- Bradycardia and AV Block with the first dose – see 'first dose' section.
- Hypertension.
- Nausea and diarrhoea.
- Blurred vision and macular oedema – see follow-up and monitoring.

6.6 Switching to siponimod from other therapies

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

- **Beta interferon, fingolimod, Tecfidera or glatiramer acetate**: no wash out period is required prior to starting siponimod.
- **Natalizumab**: there must be at least two months' wash out before starting siponimod. The risk of PML must be assessed and the patient appropriately counselled.
- **Alemtuzumab, cladribine and ocrelizumab.** If these drugs have caused a profound lymphopenia, siponimod should be delayed. For discussion at MDT.

6.7 Prescription and booking first dose

- Siponimod is prescribed via homecare, taking care to select the correct maintenance dose corresponding to genotype.
- The first dose of siponimod does not need to be supervised or given in a healthcare setting unless the patient has sinus bradycardia (heart rate <55 bpm), history of first- or second-degree [Mobitz type I] AV block,

history of myocardial infarction, or history of heart failure (patients with NYHA class I and II).

6.8 First dose administration for those at risk of bradycardia [defined in 6.7]

- Siponimod is prescribed via Epic, taking care to select the correct maintenance dose corresponding to genotype.
- R3 will hold a stock for first dose administrations.
- MS nurse collects siponimod from Outpatient Pharmacy (preferably on the day before the patient is due for admission).
- Patient attends the infusion unit in the morning. The 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.
    - Baseline 12-lead ECG.
- 12-lead ECG shown to the neurology SpR; if normal, the doctor prescribes on the Epic inpatient chart a single dose of siponimod 0.25mg orally
- 1x siponimod 0.25mg administered by nurse.
- Hourly pulse and BP recorded for six hours after the first dose.
- Follow Trust protocol if an allergic reaction or anaphylaxis occurs.
- Repeat ECG performed after six hours.
- Neurology SpR checks ECG and reviews heart rate to confirm discharge (see criteria for extended cardiac monitoring).
- Supply of siponimod for 28 days given to patient to take home.
- MS nurse sends discharge letter to GP using smartphrase and checks the plan is in place for ophthalmology review and pupil dilatation at month 3 and MS nurse follow up at month 3.

6.9 Criteria for extended cardiac monitoring

Monitor for an extra two hours if:

- heart rate at six hours is at its lowest since taking siponimod

Monitor overnight if:

- pre-existing cardiovascular problems
- new onset of second degree atrioventricular block, Mobitz Type II on ECG
- new onset third degree atrioventricular block on ECG
- symptomatic bradycardia, particularly if intervention with atropine or isoprenaline has been required
- heart rate at six hours is less than 45 beats per minute
- QTc interval is greater than 500ms on ECG

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, ensures booked for ophthalmology screening and sends patient to Ophthalmology Department (Clinic 14).
- Ophthalmology Department should have entered ophthalmology result onto Epic within two weeks; MS nurse to check. Responsibility for siponimod 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)
- Year 2 Dr (reviews skin lesions + EDSS)
- Then alternate nurse/ doctor annually if stable

Reporting of adverse events, or pregnancies on therapy, should be via Yellow Card, or to Novartis on uk.patientsafety@novartis.com.

7.2 Blood monitoring

- Month 1 and 3 (FBC, LFT), then if LFT normal six-monthly FBC and LFT.
- Absolute lymphocyte counts <0.2 $x10^9$/l, if confirmed, should lead to dose reduction to 1mg, because in clinical studies siponimod dose was reduced in patients with absolute lymphocyte counts <0.2 $x10^9$/l. Confirmed absolute lymphocyte counts <0.2 $x10^9$/l in a patient already receiving siponimod 1 mg should lead to interruption of siponimod therapy until the level reaches 0.6 $x10^9$/l when re-initiation of siponimod can be considered. If confirmed, monitor the FBC and patient closely for signs of infection (including PML) and consider suspending siponimod.
- Suspend siponimod if serum hepatic transaminases 5x upper limit of normal. If there is doubt that siponimod was the cause and LFT recovers, can restart siponimod and monitor closely.
- If no symptoms of liver injury [jaundice, nausea, vomiting] and ALT greater than 3x ULN but less than 5x ULN, and bilirubin normal, continue siponimod and monitor more frequently.

7.3 Treatment breaks/ missed doses

During the first six days of treatment, if a titration dose is missed on one day treatment needs to be re-initiated with a new titration pack.

If maintenance treatment is interrupted for four or more consecutive daily doses, siponimod needs to be re-initiated with a new titration pack.

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 siponimod.
- Unacceptable adverse effects.
- Allergic reaction to siponimod.
- Macular oedema.
- Unresolved brady-arrhythmia.
- Pregnancy and breastfeeding.
- Confirmed absolute lymphocyte counts <0.2 $x10^9$/l in a patient already receiving siponimod 1mg.
- 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 comply with monitoring and/or 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 the MS team.

10 References

National Institute for Health and Care Excellence. (2020). Siponimod for treating secondary progressive multiple sclerosis Technology appraisal guidance [TA656] Published: 18 November 2020

Novartis Pharmaceuticals UK Ltd. Mayzent -Summary of product characteristics [2021] Retrieved from: https://www.medicines.org.uk

Kappos L, EXPAND Clinical Investigators. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. 2018 Mar 31;391(10127):1263-1273.

Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

Disclaimer

It is **your** responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

Document management

Approved by:	Paul Worth		
Approval date:	08 February 2022		
JDTC approval date:	08 February 2022		
Owning department:	Neurology		
Author(s):	Alasdair Coles		
Pharmacist:	Fran Smith		
File name:	Siponimod protocol Version1 February 2022		
Supersedes:	n/a (new document)		
Version number:	1		
Local reference:		Document ID:	102443