CLINICAL GUIDELINE

Siponimod for Secondary Progressive Multiple Sclerosis

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Does this version include changes to clinical advice:	No
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Approval Group:	Medicines Utilisation Subcommittee of ADTC

Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

NHS Greater Glasgow and Clyde
Institute of Neurological Sciences
Protocol for use of Siponimod in Secondary Progressive Multiple Sclerosis

Background:

Siponimod (Mayzent®) is accepted for use within NHS Scotland for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses (in the past 1 year) and / or imaging features of inflammatory activity. This will be defined as new T2 lesions / contrasting enhancement / enlarging T2 lesion on MRI scan (at least one lesion within 1 year).

In a randomised, double-blind, placebo-controlled phase III study, siponimod was associated with a reduction in disability progression confirmed after 3 months in patients with SPMS. Siponimod reduced the risk of 6-month confirmed disability progression by 26% compared to placebo.

Agent and route:

250 microgram + 2mg film coated tablet for oral administration

Patient population applicable to:

Patients will be identified from Consultant or MS nurse led clinics.

When considering patients older than 65, it is important to note that no study data exists in this group of patients. Patients over 65 are likely to have significant co-morbidities and the risk of infections may be higher due to immunosenescence. The risk of malignancies also increases with age. Patients over 65 years will be discussed at the complex case meeting.

Authorised and Designated Areas applicable to:

Treatment with siponimod is restricted to prescription and supervision by physicians experienced in the management of MS. This may also include designated non-medical prescribers. Ongoing prescribing and monitoring will be undertaken in Acute Sector.

Indication and place in therapy:

Siponimod is the first and only oral disease modifying treatment specifically indicated for patients with SPMS with active disease in Europe. Siponimod is not used in combination with other DMTs.

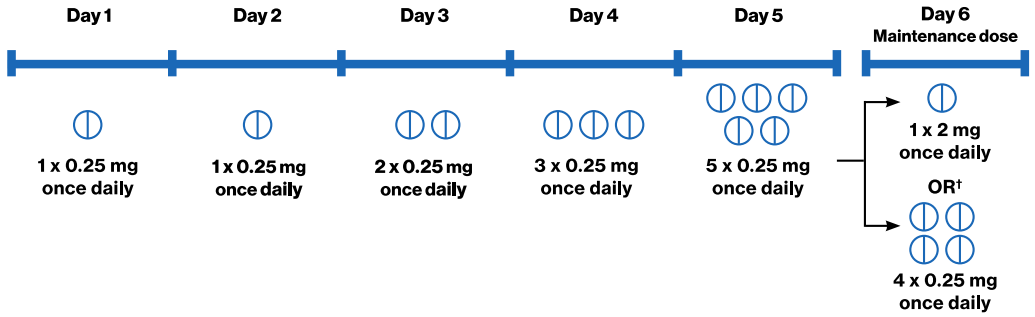
Dose, duration and administration:

Before initiation of siponimod, patients must be genotyped for CYP2C9 to determine their CYP2C9 metaboliser status. This test can be performed on blood sample. This confirms whether they are able to receive siponimod and defines the dose they should receive.

Metaboliser level	CYP2C9 genotype	Maintenance dose
Extensive metabolisers	CYP2C9*1*1	2 mg
	CYP2C9*1*2	2 mg
Intermediate metabolisers	CYP2C9*2*2	2 mg
	CYP2C9*1*3	1 mg
Poor metabolisers	CYP2C9*2*3	1 mg
	CYP2C9*3*3	Siponimod should not be given

Treatment Initiation

Initiation of treatment with siponimod results in a transient decrease in heart rate. For this reason, a gradual 5 day titration is required. A titration pack will be provided to the patient through Homecare pharmacy. This contains 12 film-coated tablets in a wallet.

	The same titration pack is used for patients where the recommended maintenance dose is 1mg daily or 2mg daily. (Additional exposure of 0.25mg on day 5 does not compromise patient safety regardless of CYP genotype).  †Maintenance dose is dependent on the results of the patient's genotype test
Monitoring:	**<u>Baseline screening</u>** • Genetics (through Viapath Analytics LLP) • Routine bloods (U+Es, LFTs, FBC) within last 6 months • Electrocardiogram (ECG) • HIV and Hepatitis screening bloods. • Varicella antibodies, if negative vaccinate (wait at least 4 weeks after second vaccine before starting siponimod) • Pregnancy test as relevant **<u>First Dose Observation</u>** Patients with the following cardiac conditions should be observed during initiation and for a period of 6 hours after the first dose of siponimod for signs and symptoms of bradycardia: • sinus bradycardia (heart rate < 55 bpm) • history of first- or second-degree (Mobitz type) atrioventricular (AV) block • history of myocardial infarction • history of heart failure (NYHA class I and II). In these patients, an ECG should be obtained prior to dosing and at the end of the observation period with blood pressure and heart rate monitoring throughout. This will take place in neurology day ward 53. If required on-call cardiology can be contacted. **<u>During treatment</u>** • Routine bloods (U+Es, LFTs, FBC) at months 1, 3, 6, 9, 12 then 6-monthly • Macular screening at 3 to 4 months • Skin cancer awareness • Blood pressure measurement during monitoring visits **Surveillance and stopping criteria** Patients will receive surveillance MRI scan of brain +/- spine annually, safety blood monitoring, regular review with MSSN and Consultant Neurologist. If a patient develops any conditions listed in the contraindications section, if there is treatment failure or the clinician deems the risk of adverse effects are higher than the potential benefits of continuing treatment.
Missed Doses	**Missed dose(s) during treatment initiation** During the first 6 days of treatment, if a titration dose is missed on one day treatment needs to be re-initiated with a new titration pack.

	Missed dose after day 6 If a dose is missed, the prescribed dose should be taken at the next scheduled time; the next dose should not be doubled. **Re-initiation of maintenance therapy after treatment interruption** If maintenance treatment is interrupted for 4 or more consecutive daily doses, siponimod needs to be re-initiated with a new titration pack.
Contraindications:	• Patients who in the previous 6 months had a myocardial infarction (MI), unstable angina pectoris, stroke of 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 have a pacemaker. • Substantial immunological, cardiological or pulmonary conditions • Ongoing macular oedema • Uncontrolled diabetes • Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser) • Varicella antibody negative status • History of symptomatic bradycardia or recurrent syncope • Uncontrolled hypertension (systolic >150 and diastolic > 90 mmHg) • Severe untreated sleep apnoea • Hypersensitivity to peanut, soya or other excipients (listed in SPC) • Immunodeficiency syndrome • Active malignancy • Severe liver impairment (Child Pugh class C) • Pregnancy and in women of childbearing potential not using effective contraception • History of progressive multifocal leukoencephalopathy or cryptococcal meningitis. *Please refer to Summary of Product Characteristics for more information*
Drug Interactions	• Patients taking class 1a (quinine, procainamide) or class III (amiodarone, sotalol) anti-arrhythmic • Heart rate lowering Calcium channel blockers (verapamil, Diltiazem), and other heart rate lowering drugs (Ivabradine, Digoxin) Siponimod is metabolised by the cytochrome P450 pathways (mainly CYP2C9) but also CYP3A4. Caution is needed when prescribing siponimod with drugs that interact with these pathways. *Please note this list is not exhaustive. Refer to SPC for full information or Stockley's Drug Interactions at https://www.medicinescomplete.com/#/interactions/stockley*
Cautions:	• Diabetes mellitus • Uveitis • Existing retinal disease • Co-prescribing of immunomodulatory treatments • Those driving heavy vehicles and public vehicles need to bear caution with 2% seizure risk and seek further advice from DVLA.

Adverse effects:	Raised liver enzymes (12%), Hypertension (12%), Herpes viral infection (5%), Zoster (2%), Lymphopenia (1%), peripheral oedema (5%), Macular Oedema (2%), Seizures (2%), Bradycardia during initiation (3%), Alanine amino transferase increased (1%) *For full list of adverse effects, see Summary of Product Characteristics.*
Service requirements	**Metaboliser Status Genotype Test** A pre-paid blood test, including correct packaging and postage, to collect a patient's sample and a metaboliser status genotype test, using a third party laboratory (Viapath) to determine the patient's variation of the CYP2C9 genotype. The results will be emailed to clinician(s), with turnaround time less than a week.
Licensed status:	Licensed medicine.
Authorised prescribers:	Consultant Neurologists with specialist interest in Multiple Sclerosis Designated non-medical prescribers (e.g. clinical nurse specialist, pharmacist, physiotherapist)
References:	Mayzent Summary of Product Characteristics https://www.medicines.org.uk/emc/product/11020/smpc Scottish Medicines Consortium (SMC) https://www.scottishmedicines.org.uk/medicines-advice/siponimod-mayzent-full-smc2265/
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