Prescribing MIDODRINE for the treatment of Severe Orthostatic Hypotension due to Autonomic Dysfunction, Postural Orthostatic Tachycardia Syndrome (POTS) or Inappropriate Sinus Tachycardia (IST)

At present there are no approved medicines for the treatment of POTS or IST and therefore in these circumstances, midodrine is prescribed for an unlicensed indication. Treatments must be tailored to each patient, taking into account the cause of their syndrome and their symptoms, since the same medicines can have very different effects on different individuals

Midodrine is a pro-drug which is converted to the active metabolite, desglymidodrine, an alpha adrenergic agonist. This causes peripheral arterial and venous constriction, producing an increase in vascular tone and blood pressure (BP).

In South London, midodrine is considered as a treatment option for

a) **Licensed indication (Bramox® brand): Severe Orthostatic Hypotension due to Autonomic Dysfunction** when corrective factors have been ruled out and other forms of treatment are inadequate.

b) **Unlicensed indication: Postural Orthostatic Tachycardia Syndrome (POTS) and Inappropriate Sinus Tachycardia (IST),** following failure of simple methods to control symptoms (fluid, exercise, and compression clothing). Midodrine is suitable for patients with low BP associated with symptoms of POTS such as palpitations, hypotension associated with dizziness, light-headedness and near syncope, dyspnoea, hyperventilation, low exercise tolerance, fatigue, insomnia and anxiety.

Additional resources have been developed to support implementation including:

- Notification of initiation of midodrine for the treatment of severe orthostatic hypotension, POTS and IST. This document **must be completed and sent to the General Practitioner (GP) on initiation**.
- Transfer of prescribing responsibility to primary care for midodrine. This document **must be completed and sent to the GP when transferring the prescribing responsibility** in accordance with South London guidelines.

Where midodrine is used for unlicensed indications: Treatment must be initiated by a cardiology specialist, after careful evaluation of the overall balance of the patient's expected benefits and risks. The initiating clinician / organisation is responsible for ensuring the patient is provided with a structured support process (including availability of contact numbers for specialist nurses), follow-up and the supply of midodrine for the first three months of treatment or until the dose is stable. During this time, efforts should be made to reinforce adherence and address any adverse effects.

Transfer of prescribing responsibility to patients own GP

Following the initial 3 month period and when the patient is on a stable dose of midodrine, prescribing responsibility may be considered for transfer to the patient's own GP, when the consultant and the GP are in agreement that the patient's condition is stable or predictable. Transfer of prescribing responsibility should be followed and appropriate documents completed and forwarded to the GP to ensure seamless care.

Contraindications (for full details see BNF or **SPC**)	**Cautions** (for full details BNF or **SPC**)
• Hypersensitivity to the active substance or to any of the excipients • Severe organic heart disease (such as bradycardia, heart attack, congestive heart failure, cardiac conduction disturbances or aortic aneurysm) • Serious obliterative blood vessel disease, cerebrovascular occlusions and vessel spasms • Hypertension • Serious prostate disorders • Urinary retention • Severe renal impairment (CrCl< 30ml/min) or acute kidney disease • Proliferative diabetic retinopathy • Pheochromocytoma • Hyperthyroidism/ thyrotoxicosis • Narrow angle glaucoma • Pregnancy or women of childbearing potential not using contraception measures • Breastfeeding • For contraindications for use with other medicines see overleaf	• Severe orthostatic hypotension with supine hypertension • Severe disturbances of the autonomic nervous system • Atherosclerotic disease especially with symptoms of intestinal angina or claudication of the legs • Hepatic impairment - due to lack of clinical data • Mild to moderate renal impairment (CrCl 30 to 89ml/min) – due to lack of clinical data close monitoring is recommended • For cautions for use with other medication – see overleaf

Note: BNF=British National Formulary**; SPC=**Summary of Product Characteristics

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Approved by Croydon Prescribing Committee Sep 2019 (Review date: Sep 2021)
Original Document: South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: Bexley/ Bromley/ Greenwich/ Lambeth/ Lewisham & Southwark Clinical Commissioning Groups (CCGs) & GSTFT/KCH/SLAM/Oxleas NHS Foundation Trusts & Lewisham & Greenwich NHS Trust
Approved January 2018 (version 3) Review date January 2020

Dosing

For severe orthostatic hypotension due to autonomic dysfunction, **the initial recommended dose is 2.5mg three times a day** with or without food**.** Depending on the supine and standing BP readings, the dose may be increased weekly to achieve optimal control of symptoms, to a maximum dose of 10mg three times a day.

For POTS or IST, **the initial recommended dose is 2.5mg three times a day** with or without food, titrated at intervals of more than 3 days until optimal response in obtained. The normal recommended maximum dose is 30mg daily - **Doses in excess of 40mg daily are not recommended.** Upon escalating the dosage, the supine and standing BP should be closely monitored. Most patients are controlled at or below 30mg/day given in 3 or 4 divided doses, but midodrine can be given up to six times daily if required to give adequate control of symptoms.

The last daily dose should be taken at least 4 hours before bedtime to reduce the risk of supine hypertension.

- There is limited data on dosing in elderly patients and SPC recommends cautious dose titration.
- There are no specific studies that have focused on a possible dose reduction in patients with renal impairment. Midodrine is contra-indicated in severe renal dysfunction (CrCl<30ml/min) and acute renal failure.

Monitoring

- Midodrine can increase supine BP as well as result in a postural BP drop. Regular monitoring of supine, standing and sitting BP (for 2 to 3 minutes) is required, usually every 3 months or more frequently if recommended by the cardiologist and if symptoms recur. Increases in supine BP will require a dose reduction or cessation of therapy - Seek specialist advice.
- Renal[i] and liver function should be monitored before starting treatment with midodrine then at least annually throughout therapy, or more frequently if clinically indicated.

Side effects (for full details see the BNF or SPC)

- Supine hypertension is a common side effect and can be a dose dependent effect. Patients should be told to monitor and report the following symptoms immediately: cardiac awareness (chest pain, palpitations, and shortness of breath), headache and blurred vision. To prevent supine hypertension, patients should be advised to take their last daily dose at least 4 hours before bedtime. The risk of supine hypertension occurring at night can be also be reduced by elevating the head. Reduction in the midodrine dose may help control supine hypertension, but if it does not resolve, then midodrine must be stopped.
- The most frequent and very common side effects include: piloerection, pruritus (mainly of the scalp), paraesthesia, headache, nausea, dyspepsia, stomatitis, dysuria, urinary disorders, chills, flushing and/ or rash.

Drug Interactions (for full details on drug interactions – see BNF or SPC)

Drug / Drug class	Recommendation
Sympathomimetics and other vasoconstrictive substances such as reserpine, guanethidine, tricyclic antidepressants, antihistamines, thyroid hormones and MAO-inhibitors	Concomitant use should be avoided as these can cause a pronounced increase in BP.
Alpha-adrenergic antagonists such as prazosin and phentolamine	Concomitant use should be avoided as these can antagonise the effects of midodrine.
Cardiac glycosides (digoxin, digitoxin)	Concomitant use is not recommended as the heart rate reducing effect may be potentiated and heart block can occur.
Drugs that directly or indirectly reduce heart rate	Caution is advised. Monitor heart rate and check for signs and symptoms of bradycardia as midodrine can potentiate bradycardia
Corticosteroids	Concomitant use can potentiate or enhance corticosteroids hypertensive effects.
Mineralocorticoids or glucocorticoids (e.g. fludrocortisone)	Concomitant use may increase risk of glaucoma or increase intraocular pressure and should be carefully monitored.
Drugs metabolised by CYP2D6 enzyme (e.g. promethazine)	Concomitant use can reduce their clearance and enhance their effect.

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
• To initiate midodrine in line with local guidance – For unlicensed indication(s) notify GP that midodrine has been prescribed using the notification of initiation document. • To ensure patient has consented to treatment and, where appropriate, is aware the use is for an unlicensed indication. • To provide counselling to improve adherence and address any adverse effects (including advice on dosage, frequency and the risks and benefits of treatment). • As part of self-monitoring, patient should be recommended to use BP monitors approved by the British Hypertension	• To ensure use of midodrine is in line with local guidance • To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation and in line with the transfer of care guidance). • To provide on-going prescriptions for midodrine after 3 months and is prescribed a stable dose. • To monitor BP every 3 months *(Note: patient's home BP readings can be considered - if using validated and approved BP monitors and are competent in measuring BP).* Seek advice from the specialist if BP rises

Society (BHS) and provided with appropriate training on how to measure their BP. • Perform baseline monitoring tests: BP (supine, sitting and standing), baseline renal and liver function. • For unlicensed indication(s), the patient is provided with contact information for specialist nurse advice during normal working hours. • For unlicensed indication(s), supply midodrine for at least the first 3 months of therapy and/ or until the patient is on a stable dose. • Following the initial three months of treatment and when the dose is stable, transfer prescribing responsibility to the GP using local transfer of prescribing responsibility document. • Provide the GP with relevant specialist contact information should further assistance be required during working hours. • To review patient at the request of GP should any problems arise (side-effects / lack of efficacy). • To review therapy at least annually and communicate promptly with the GP if treatment is changed.	consistently more than 20mmHg or where symptoms of orthostatic hypotension return. • Review renal and liver function at least annually, more frequently if clinically indicated. • To monitor the patient for adverse effects and control of symptoms. • To report and seek advice regarding any concerns, for example: side-effects, co-morbidities, pregnancy, or lack of efficacy to the specialist team. • To advise the specialist if non-adherence is suspected. • To refer back to specialist if the patient's condition deteriorates or treatment fails. • To stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.

Note: A combination treatment with midodrine and ivabradine is prescribed in a few patients for treatment of POTS and/ or IST

References

1. Summary of Product Characteristics, Bramox® Updated May 2016 Midodrine (Bramox®) http://www.mhra.gov.uk/spc-pil/?subsName=MIDODRINE%20HYDROCHLORIDE&pageID=SecondLevel
2. NICE Evidence Summary: Orthostatice hypotension due to autonomic dysfunction: midodrine. [ESNM61] October 2015. Accessed via https://www.nice.org.uk/advice/esnm61/chapter/Key-points-from-the-evidence
3. Ross AJ, Ocon AJ, Medow MS *et* al. A double-blind placebo-controlled cross-over study of the vascular effects of midodrine in neuropathic compared with hyperadrenergic postural tachycardia syndrome. Clinical Science 2014;126(4):289-96
4. Ross AJ; Ocon AJ; Medow MS; Stewart JM. Therapies for postural tachycardia syndrome in children Zhonghua er ke za zhi. Chinese journal of pediatrics, 2011;49(6):428-432),
5. Zhang FW.; Liao Y.; Li XY; *et al*. Effect of selective alpha1 receptor agonist in the treatment of children with postural orthostatic tachycardia syndrome. Chinese journal of pediatrics, 2008;46(9):688-691
6. Chen L.; DU J.B.; Jin H.F.; *et al*. Midodrine hydrochloride is effective in the treatment of children with postural orthostatic tachycardia syndrome. Circuion 2011;75(4);927-931)
7. Chen L; Wang L; Sun J; *et* al. Outcomes in adolescents with postural orthostatic tachycardia syndrome treated with midodrine and beta-blockers. Pacing and Clinical Electrophysiology 2009; 32(2):234-238
8. Lai CC.; Fischer PR.; Brands CK.; et al. Effects of volume loading and pressor agents in idiopathic orthostatic tachycardia.Circulation 1997;96:575–80

[i] Estimate creatinine clearance (CrCl) using the Cockcroft-Gault equation.

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Notification of Initiation to GP

- **The checklist must be completed and sent to the GP when MIDODRINE therapy is initiated for the above indications**
- **Following a 3 month period, if the patient is on a stable dose and treatment is to continue, care may be transferred to the GP. At this point, a transfer of prescribing responsibility document should be completed and sent to the GP**

Patient Details	**GP Details**
Surname:	Name:
Forename:	Address:
Address:	
	Postcode:
Postcode:	Tel:
NHS No:	NHS.net email:
DOB: Sex: Male / Female	

Date of Diagnosis:

Indication (Tick as appropriate)

- ☐ **Severe orthostatic hypotension due to autonomic dysfunction**
- ☐ **Postural Orthostatic Tachycardia Syndrome (POTS)**
- ☐ **Inappropriate Sinus Tachycardia (IST)**

Initiation Dosing Regimen

Baseline Monitoring		
	Results	**Date of test**
Supine Blood Pressure		
Standing Blood Pressure		
Sitting Blood Pressure		
Serum Creatinine		
Creatinine Clearance*		
Aspartate Transaminase (AST) or Alanine Transaminase (ALT)		

*Estimate creatinine clearance (CrCl) using the Cockcroft-Gault equation

Further Relevant Information

Patient Information ***NOTE: Must be yes for ALL statements for transfer to primary care***	**Yes**	**No**
1. Patient has consented to the use of midodrine including, where appropriate, the unlicensed indication		
2. Patient is aware of the benefits and risks of midodrine therapy for their condition		
3. Patient is aware of dosing instructions and that the last dose should be taken **at least four hours before bedtime** to reduce the risk of supine hypertension		
4. Patient has been advised on the management of common side effects associated with midodrine		
5.Patient has access to specialist nursing support (including contact numbers) if unlicensed use		

AUTHORISATION (medical practitioner undertaking assessment)

Signature: **Print name:**

Position: **Organisation:**

Contact number: **Date:**

Approved by Croydon Prescribing Committee Sep 2019 (Review date: Sep 2021)
Original Document: South East London Area Prescribing Committee. A partnership between NHS organisations in South East London: Bexley/ Bromley/ Greenwich/ Lambeth/ Lewisham & Southwark Clinical Commissioning Groups (CCGs) & GSTFT/KCH/SLAM/Oxleas NHS Foundation Trusts & Lewisham & Greenwich NHS Trust
Approved January 2018 (version 5) Review date January 2020

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Transfer of Prescribing Responsibility

Section A: To be completed by the initiating organisation / clinician INITATING ORGANISATIONS TO ADD LOCAL CONTACT DETAILS FOR SPECIALIST SERVICE (TEL / EMAIL) FOR QUERIES

Patient Details:

Name:..... DOB: ..../..../.... **Hospital No: …….. NHS No: ……..**

GP Practice Details:	**Consultant Details:**
Name: ……	Consultant Name:.....
Address: ……	Organisation Name:.....
Tel no: ……	Clinic Name:……
NHS.net e-mail: ……	Address: ……
	Tel no: ..... NHS.net email: ……

Dear Dr……

This patient is on a midodrine for: Severe orthostatic hypotension due to autonomic dysfunction / Postural Orthostatic Tachycardia Syndrome (POTS) / Inappropriate Sinus Tachycardia (IST) (delete as appropriate)

I have supplied the first three months of therapy for this patient and the dose of midodrine is now stable. I am requesting your agreement to transfer the prescribing responsibility for this patient's on-going treatment from …/…/… in accordance with the South East London Area Prescribing Committee (SEL APC) formulary recommendations.

I will review the patient at least annually throughout treatment. The following investigations have been performed and are acceptable for transfer of care.

Test	Result	Date of test	Please repeat test in:
Supine Blood Pressure			Months
Standing Blood Pressure			Months
Sitting Blood Pressure			Months
Serum Creatinine			Months
Creatinine Clearance*			
Aspartate Transaminase (AST) or Alanine Transaminase (ALT)			Months

*Estimate creatinine clearance (CrCl) using the Cockcroft-Gault equation

Contact details of specialist nurse for GPs to access:

Name: …….. Tel no:……. NHS.net email: ……

Other relevant information:

……..

- I confirm that I have prescribed in accordance with the SEL APC guidelines ☐
- I confirm the patient has consented to treatment ☐
- I confirm that the patient has been made aware of the benefits and risks of midodrine therapy, including risk of supine hypertension, and that they know how to seek medical help should symptoms occur. ☐
- I confirm that patient and/or carer is able to monitor their BP while lying, sitting and standing at home ☐
- I confirm patient has access to specialist nursing support (including contact numbers) if unlicensed ☐

Signed:……. Name of Clinician:…… Date: …….

Section B: To be completed and signed by the GP if NOT willing to take on prescribing responsibility and returned to the specialist clinician as detailed in Section A above.

This is to confirm that I am not willing to accept the transfer of care of prescribing midodrine for this patient ***for the following reason***:

……

GP name: …… GP signature: …… Date: ……/……./…....

(This transfer of care document should be reviewed in-conjunction with the drug screening checklist sent previously by the initiating clinician - if not received contact consultant named above for details)