SHARED CARE GUIDELINE FOR MIDODRINE HYDROCHLORIDE (BRAMOX® 2.5MG, 5MG TABLETS)

INDICATION

Orthostatic hypotension (or postural hypotension) is a condition in which standing leads to an abnormally large drop in blood pressure that can result in symptoms such as light-headedness, dizziness, blurring of vision, fainting and falls. Orthostatic hypotension may result from acute conditions, such as blood loss and volume depletion, or may be secondary to a disturbance in autonomic regulation seen in central or peripheral diseases of the autonomic nervous system, such as multiple system atrophy, Parkinson's disease, dementia with Lewy Bodies, pure autonomic failure, autoimmune autonomic ganglionopathy, amyloidosis and diabetic autonomic neuropathy. Orthostatic hypotension is also frequently caused by medication (e.g. antihypertensive drugs, dopamine and agonists) and/or lack of adequate fluid intake, particularly in elderly patients. However, this form of orthostatic hypotension is often overcome by adopting simple lifestyle changes alongside non-pharmacological treatments without the need for pharmacological intervention.

Midodrine hydrochloride (Bramox®) is a peripheral α-adrenergic agonist that is almost completely absorbed after oral administration and undergoes enzymatic hydrolysis to form its pharmacologically active metabolite, de-gly-midodrine. After oral or intravenous administration, it causes a modest increase in supine and standing blood pressures in healthy volunteers. In patients with orthostatic hypotension it may substantially increase blood pressure, decrease venous capacity and lower supine and standing heart rates.
Midodrine is administered orally at an initial dose of 2.5mg three times a day. Depending on the results of supine and standing blood pressure recordings, this dose may be increased up to 10mg three times a day as a maintenance dosage.

The European Federation of Neurological Societies recommends individually tailored therapy for orthostatic hypertension. Non-pharmacological management options are recommended first-line (including compression stockings, blood pressure monitoring and increased water and salt ingestion). If these do not resolve symptoms, pharmacological treatment with fludrocortisone or midodrine, alone or in combination, may be considered.

Midodrine is licensed in the UK for the treatment of orthostatic hypotension due to autonomic dysfunction, when corrective factors have been ruled out and other (non-pharmacological) forms of treatment are inadequate. Use for other types of orthostatic hypotension is off-label and not included within this shared care guideline, (these may include use in intradialytic hypotension or postural tachycardia). The most common adverse effects reported for midodrine are supine hypertension, paraesthesiae, dysuria, pilomotor reaction (goose flesh), pruritus and rashes.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of midodrine tablets (Bramox®) can be shared between the specialist setting and the patient's GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION	
Specialist Responsibilities	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	To initiate treatment where indicated, providing at least the first 28 day prescription and review for efficacy and adverse effects before considering transfer of prescribing to primary care.
3	To seek agreement from the patient's GP to transfer responsibility for prescribing.
4	To explain the possible side-effects of midodrine to the patient.
5	Ensure that the patient knows what to do and who to contact if they experience adverse events.
6	To provide the GP with appropriate prescribing information and any additional information requested.
7	To agree with the GP arrangements for ongoing monitoring to ensure the safe use of midodrine. This should include responsibility for undertaking any necessary tests as detailed below.
8	To be available for advice if the patient's condition changes.
9	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
10	To ensure the patient has given informed consent to their treatment.
11	To liaise with the GP on any suggested changes in prescribed therapy / notify GP of any changes in the patient's condition.
12	To inform the GP if it is considered appropriate to discontinue treatment.

General Practitioner Responsibilities	
1	To contact the referring consultant without delay if they do not wish to enter into a shared care agreement.
2	Where appropriate to continue prescriptions of midodrine in accordance with the instructions from the consultant.
3	To undertake ongoing monitoring as agreed with consultant, including monitoring side effects of treatment, and seek advice from the consultant if necessary.
4	To deal with general health issues of the patient.
5	To liaise with the consultant regarding any complications of treatment.
6	To check for possible drug interactions when newly prescribing or stopping concurrent medication.

Patient's (or carer's) role	
1	Report to the specialist or GP if he/she does not have a clear understanding of the treatment.
2	Attend appropriate consultant and GP appointments.
3	To have any required monitoring/tests carried out at regular intervals, as appropriate.
4	Share any concerns in relation to treatment with midodrine.
5	Seek help urgently if suspected side effects appear, or otherwise unwell.

SUPPORTING INFORMATION

Monitoring

- Evaluate renal and hepatic function before starting treatment and every 6 months when on long term treatment.
- Monitor for signs or symptoms of bradycardia at review and on an ad hoc basis.
- Monitor supine and standing blood pressure (due to the risk of hypertension in the supine position) every 6 months.
- Monitor for symptoms of supine hypertension such as chest pain, palpitations, shortness of breath, headache and blurred vision, and advise patients to self-monitor and report immediately.
- Advise patients to report symptoms of supine hypertension immediately.

Dosage and Administration

Initial dose: 2.5 mg three times a day.

Depending on the results of supine and standing blood pressure recordings, this dose may be increased weekly up to a dose of 10 mg three times a day. This is the usual maintenance dosage.

The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension.

Midodrine 5 mg tablets may be taken with food

Contraindications

- Severe organic heart disease (e.g. bradycardia, heart attack, congestive heart failure, cardiac conduction disturbances or aortic aneurysm).
- Hypertension.
- Serious obliterative blood vessel disease, cerebrovascular occlusions and vessel spasms.
- Acute kidney disease.
- Severe renal impairment (creatinine clearance of less than 30 ml/min).
- Serious prostate disorder.
- Urinary retention.
- Proliferative diabetic retinopathy.
- Pheochromocytoma.
- Hyperthyroidism.
- Narrow angle glaucoma.
- Hypersensitivity to the active substance or to any of the excipients

Cautions

<u>Severe orthostatic hypotension with supine hypertension</u>

Regular monitoring of supine and standing blood pressure is necessary due to the risk of hypertension in the supine position, e.g. at night. Patients should be told to report symptoms of supine hypertension immediately. Supine hypertension may often be controlled by an adjustment to the dose. If supine hypertension occurs, which is not overcome by reducing the dose, midodrine must be stopped.

Avoid administration in the late evening. The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension. The risk of supine hypertension occurring during the night can be reduced by elevating the head.

Severe disturbances of the autonomic nervous system
In patients suffering from a severe disturbance of the autonomic nervous system, administration of midodrine may lead to a further reduction of blood pressure when standing. If this occurs, midodrine should be stopped.

Atherosclerotic disease
Caution must be observed in patients with atherosclerotic disease especially with symptoms of intestinal angina or claudication of the legs.

Prostate disorders
Caution is advised in patients with prostate disorders, as midodrine may cause urinary retention.

Renal and hepatic function
Midodrine is contraindicated in patients with acute renal impairment or severe renal impairment. Treatment with midodrine has not been studied in patients with hepatic impairment. Evaluate the renal and hepatic parameters before starting treatment with midodrine and on a regular basis.

Heart rate
Bradycardia may occur after midodrine administration, due to vagal reflex. Caution is advised when midodrine is used concomitantly with cardiac glycosides (such as digitalis preparations) and other agents that directly or indirectly reduce heart rate. Monitor for signs or symptoms suggesting bradycardia.

Side effects

The most common adverse effects were piloerection, itchy scalp, paraesthesia, paraesthesia of the scalp, urinary retention, supine hypertension, increased supine hypertension, and pruritus.

Interactions

Concomitant treatment with sympathomimetics and other vasoconstrictive substances such as reserpine, guanethidine, tricyclic antidepressants, antihistamines, thyroid hormones and MAO-inhibitors, including treatments that are available without prescription, should be avoided as a pronounced increase in blood pressure may occur.
As with other specific α-adrenergic agonists, the effect of midodrine is blocked by α-adrenergic antagonists such as prazosin and phentolamine.
Monitoring is recommended if midodrine is combined with other drugs that directly or indirectly reduce the heart rate.
Simultaneous use of digitalis preparations is not recommended, as the heart rate reducing effect may be potentiated by midodrine and heart block may occur.
Midodrine may potentiate or enhance the hypertensive effects of corticosteroid preparations. Treatment with midodrine in combination with mineralocorticoids or glucocorticoids (e.g. fludrocortisone) may increase the risk of glaucoma/increased intraocular pressure. Monitor patients.
The potential for pharmacokinetic interaction is limited as the metabolic pathways do not involve cytochrome P450 enzymes. However, decreased clearance of medicinal products metabolised by CYP2D6 (e.g. promethazine) has been reported.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs:
Bramox® 5mg tablets cost £75.05 for 100 tablets (75p per tablet). A dose of 10 mg taken 3 times a day costs £5.50/day.
Bramox® 2.5mg tablets cost £55.05 for 100 tablets (55p per tablet). A dose of 2.5 mg taken 3 times a day costs £1.65/day.

References

Summary of Product Characteristics. Bramox®. Brancaster Pharma Ltd. Accessed via www.mhra.gov.uk on 5th October 2015

National Institute of Health and Care Excellence. ESMN61. Orthostatic hypotension due to autonomic dysfunction: midodrine. October 2015. Accessed via www.nice.org.uk on 12th October 2015

National Institute for Health and Research. Horizon Scanning Research & Intelligence Centre. Midodrine (Bramox) for orthostatic hypotension. May 2015. Accessed via www.hsric.nihr.ac.uk on 5th October 2015

eMC Dictionary of Medicines and Devices Browser. Accessed via http://dmd.medicines.org.uk/ on 5th October 2015

NHS Business services authority. NHS prescription services. NHS electronic drug tariff. Accessed via www.drugtariff.nhsbsa.nhs.uk on 5th October 2015

Papworth Hospital NHS Foundation Trust. Midodrine SCG: For patients with idiopathic orthostatic hypotension or neurocardiogenic syncope.V 4.1 Accessed via www.cambsphn.nhs.uk on 12th October 2015

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