MIDODRINE [BRAMOX®] for SEVERE ORTHOSTATIC HYPOTENSION

Shared Care Agreement (SCA): For the use of midodrine [2.5mg tablets, 5mg tablets] for the management of severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines how the responsibilities for managing the prescribing of midodrine for the treatment of severe autonomic orthostatic hypotension, a rare and often debilitating form of postural hypotension, can be shared between the specialist and general practitioner (GP). GPs are invited to participate. In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners in circumstances of shared care, the Department of Health has advised that the legal responsibility for prescribing lies with the doctor who signs the prescription. 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 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 between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

Bramox® is the first licensed presentation of midodrine available in the UK and was available since July 2015. The Shared Care Guidelines in this document therefore relate to the approved SmPC for Bramox®. Prescribing Bramox® ensures that patients receive a quality-approved UK formulation with the associated Patient Leaflet, and avoids the risks, liabilities and responsibilities of an unlicensed formulation of midodrine being dispensed instead of Bramox®.

RESPONSIBILITIES and ROLES

<table>
<thead>
<tr>
<th>Specialist responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Confirm the diagnosis of severe orthostatic hypotension due to autonomic dysfunction and assess whether the patient is suitable for treatment, including the baseline assessment of renal and liver function.</td>
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<tr>
<td>2 Initiate treatment and continue to supply the drug until the patient has achieved a suitable and effective maintenance dose.</td>
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<tr>
<td>3 Monitor the patient’s blood pressure carefully during the initiation and dose titration period and ensure that there is a system in place for checking the supine and standing blood pressure frequently during this period. Ambulatory blood pressure monitoring may be recommended for some patients in the first month of treatment / after any significant changes in dose.</td>
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<tr>
<td>4 Assess whether the patient is tolerating therapy, address any adverse effects and check adherence to treatment.</td>
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<td>5 Assess response to treatment after 8-12 weeks of therapy and, if effectively controlling symptoms and the patient is tolerating therapy, consider asking the GP if they are willing to participate in a shared care agreement.</td>
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<td>6 Communicate any relevant information, including baseline tests and results to the GP at the point of transfer of prescribing responsibility.</td>
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<td>7 Throughout therapy, assess the patient for suitability for on-going treatment, considering whether the treatment should be modified or discontinued at six and twelve months following initiation and then annually thereafter, unless the clinical condition requires more frequent review.</td>
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<td>8 Communicate promptly to the GP any changes in treatment, results of any monitoring undertaking and adverse effects experienced.</td>
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<tr>
<td>9 Provide the patient and GP with relevant contact information with clear arrangements for back up advice and support should further assistance be required relating to the drug.</td>
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General Practitioner responsibilities

1. Notify the consultant promptly of agreement to shared care
2. Take over the prescribing of midodrine after receiving communication from the specialist and once the patient has been stabilised on a maintenance dose
3. Review the patient regularly throughout therapy including checking postural blood pressure (at least three monthly but more frequently should symptoms recur), renal and liver function (3 monthly or more regularly if clinically indicated).
4. Refer back to the specialists if the condition deteriorates or there are any issues or concerns during therapy, specifically where the supine blood pressure rises by more than 20mmHg or where the symptoms of postural hypotension recur.
5. Avoid the co-prescription of alpha-blocking drugs, such as doxazocin, prazosin or phentolamine, as these may reduce the efficacy of midodrine
6. Stop treatment in the event of a severe adverse effect and seek advice from the specialist. Report any suspected adverse effects experienced during treatment to the MHRA.

Patient's role

1. Ensure they have a clear understanding of the treatment
2. Attend for the required monitoring throughout therapy
3. Ensure that they take their last dose in the evening at least four hours before going to bed. Report any suspicion of high blood pressure when lying down in bed at night.
4. Report any suspected adverse effects, or other concerns, to their GP or specialist.

BACK-UP ADVICE AND SUPPORT

<table>
<thead>
<tr>
<th>Contact details</th>
<th>Telephone No.</th>
<th>Bleep:</th>
<th>Fax:</th>
<th>Email address:</th>
</tr>
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<tbody>
<tr>
<td>Specialist clinician</td>
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<tr>
<td>Specialist Nurse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacist / Hospital Pharmacy Dept:</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
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</table>
SUPPORTING INFORMATION

Licensed indications
Treatment of adults with severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate.¹

Evidence Base
Two double-blinded randomised controlled trials (RCTs)²,⁳ provided evidence that midodrine improves patient-rated symptoms of postural hypotension, such as syncope (fainting) and low energy levels. The evidence showed that 10 mg midodrine taken orally 3 times a day for 3 to 4 weeks increases standing blood pressure 1 hour post-dose more than placebo in people with symptomatic postural hypotension due to dysfunction in the autonomic nervous system. These findings were confirmed in other clinical studies showing improvement in standing blood pressure and in patient symptoms.

Dosage and Administration
Initially: 2.5mg three times daily. Depending on the results of supine and standing blood pressure, this dose may be increased weekly up to a dose of 10mg three times daily. This is the usual maintenance dosage. Doses in excess of 30mg per day are unlicensed and should always be on the recommendation of a specialist. A careful evaluation of the response to treatment and of the overall balance of the expected benefits and risks needs to be undertaken before any dose increase and advice to continue therapy for long periods.

Contraindications
- Severe organic heart disease (e.g. bradycardia, heart attack, congestive heart failure, cardiac conduction disturbances or aortic aneurysm).
- Hypertension.
- Serious obliterator 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

Monitoring
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 such as chest pain, palpitations, shortness of breath, headache and blurred vision, and should be monitored for these side effects by the treating physician. Supine hypertension may often be controlled by an adjustment to the dose. If supine hypertension (systolic BP>160mmHg) occurs, which is not overcome by reducing the dose, treatment with midodrine must be stopped.

The time of administration of the drug is important in this context. 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.

Adverse Effects
The most frequent adverse reactions relating to midodrine therapy are piloerection, pruritus of the scalp and dysuria which occur very commonly. Supine hypertension may occur and is dose-related.

Other side effects include:
- Cardiovascular: Palpitations, tachycardia, reflex bradycardia, arrhythmias and supine hypertension

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- Gastrointestinal: nausea/dyspepsia, vomiting
- Urinary: urinary retention and dysuria
- CNS: headache, restlessness, excitability, irritability, light-headedness or dizziness

See the **Summary of product characteristics** for a complete list of adverse effects.

**Drug Interactions**

**Sympathomimetics and other vasopressor agents**

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.

**Alpha-adrenergic antagonists**

As it is an α-adrenergic agonist the effect of midodrine is blocked by α-adrenergic antagonists such as doxazosin, prazosin and phentolamine.

**Heart rate reducing drugs**

Monitoring is recommended if midodrine is combined with other drugs that directly or indirectly reduce the heart rate such as cardiac glycosides. Simultaneous use of digitalis preparations, such as digoxin, is not recommended, as the heart rate reducing effect may be potentiated by midodrine and heart block may occur.

**Corticosteroid preparations**

Midodrine may potentiate or enhance the hypertensive effects of corticosteroid preparations. Patients being treated with midodrine in combination with mineralocorticoids, such as fludrocortisone, or glucocorticoids may be at increased risk of glaucoma/increased intraocular pressure, and should be carefully monitored. This notwithstanding, midodrine and fludrocortisone are commonly co-prescribed.

**Potential pharmacokinetic interactions**

The potential for pharmacokinetic interaction is limited as the metabolic pathways do not involve cytochrome P450 enzymes (see section 5.2 of the SmPC). However, decreased clearance of medicinal products metabolised by CYP2D6 (e.g. promethazine) has been reported.

**Cost and Procurement**

<table>
<thead>
<tr>
<th>Brand</th>
<th>Strength</th>
<th>Pack Size (Tablets)</th>
<th>NHS List Price</th>
<th>PIP Code</th>
<th>EAN Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bramox®</td>
<td>2.5mg</td>
<td>100</td>
<td>£55.05</td>
<td>397-9945</td>
<td>5060432470005</td>
</tr>
<tr>
<td>Bramox®</td>
<td>5mg</td>
<td>100</td>
<td>£75.05</td>
<td>397-9952</td>
<td>5060432470012</td>
</tr>
</tbody>
</table>

Order via AAH or your usual wholesaler.

**References**


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