**NHS LINCOLNSHIRE in association with**
**UNITED LINCOLNSHIRE HOSPITALS TRUST**

# SHARED CARE GUIDELINE: Bramox - Midodrine 2.5mg and 5mg tablets for the treatment of severe orthostatic hypotension due to autonomic dysfunction and unlicensed use for the treatment of severe orthostatic hypotension or syncope in the absence of autonomic dysfunction

## General Principles

Shared Care Responsibilities:
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (BNF 74, September 2017 – March 2018, pg.5)
Aims:
(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.
(2) Specific shared care guidance should be available for any high cost or high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.
(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.
(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

## Further copies

Further copies of any guidelines in this series are available from members of the Optum Medicines Management and Optimisation Team

**Date of Issue: November 2018**
**Review Date: November 2020**

## Principles of shared care

NHS England published Guidance - Responsibility for Prescribing between primary, secondary and tertiary care – January 2018.
Key recommendations from guidance:

**1.0 Introduction**

1.1 Shared Care Prescribing guidelines are local policies to enable General Practitioners to accept responsibility for the prescribing and monitoring of medicines/ treatments in primary care in agreement with the initiating service.
1.4 Where possible shared acre should be disease specific rather than medicine specific and link into complement local integrated care pathways and shared acre policies. Medicines and conditions suitable for shared care will be identified by local medicines committees and will be classified as AMBER ( AMBER 1 for Lincolnshire) through the traffic light system. … However it should be remembered that the provision of shared care prescribing guidelines does not necessarily mean that the GP has to agree to accept clinical and legal responsibility for prescribing; that they should only do so if they feel clinically confident in managing that condition.

**2.3 Reasonable predictable clinical situation**

2.3.1 Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stale or predictable.

**2.4 Agreement of shared care between consultant and GP**

2.4.1 Referral to the GP should only take place once the GP has agreed in each individual case and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and that the supply arrangements have been finalised. The secondary/ tertiary provider must supply an adequate amount of the medication to cover the transition period. The patiet should then be informed to obtain further prescriptions from the GP.

**2.7 Clear definition of responsibility**

2.7.1 The areas of care for which each clinician has responsibility should be clearly defined.

**2.8 Clinical responsibility**

2.8.1 Clinical responsibility for prescribing is held by the person signing the prescription who must also ensure adequate monitoring.

**2.9 Communication network & emergency support**

2.9.1.Telephone details and (if appropriate) secure email addresses of both parties should be exchanged and recorded. This will enable the practice to access timely advice, guidance and information if problems arise, and will also enable secondary care clinicians to easily contact the GP if necessary. This should include out of hours contact numbers, how to access the on-call duty doctor. Patients and their carers should also be provided with contact details for support and help if required both in and out of hours.
2.9.2 People who are being treated on the advice of a secondary acre team, but are no longer being seen in that setting , may still need a review should problems arise. The appropriate level of care or advice should be available from the secondary care team in a timely manner without necessarily requiring a new referral.

**6.0 Monitoring**

6.0.1 All appropriate monitoring arrangements must be fulfilled. The person delivering that aspect of the shared care agreement should ensure that the resources to do this are in place in the clinical setting in which they are delivered.

## Drug Details

Approved Name: **Midodrine**
Brand Name: Bramox
Form and Strength: Tablets 2.5mg and 5mg.
**The Midotense brand of 2.5mg tablet is not approved for use, as significantly more expensive than Bramox at doses above 2.5mg.**

## Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Send a letter to the GP suggesting that shared care is agreed for this patient.
2. Ensure that the patient receives supplies of midodrine from the hospital or prescribed on FP10HP until the GP formally agrees to share care.
3. Carry out U&E's, LFTs before commencing therapy and will communicate this to the GP
4. Initiate and adjust the dose of midodrine as necessary according to clinical response.
5. Periodically review the patient's clinical condition and monitor response to treatment.
9. Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
10. Follow up any adverse drug reactions reported by the GP and report back to the GP.
11. Advise the GP in stopping treatment.

## GP Responsibilities

The GP will:

1. Notify the consultant in writing, within two weeks, if they agree to share care.
2. Monitor the patients overall health and wellbeing.
3. Monitor the patient for adverse drug reactions and remain vigilant to the risk of potential drug interaction.
4. Prescribe Bramox for the patient.
5. Carry out the following monitoring. Blood pressure checks ( supine and standing) every month. U&E's and creatinine every 3 months , LFTs every 6 months or at intervals agreed with the consultant.
6. Refer back to the specialist if condition deteriorates as advised by specialist service.
7. Report adverse events to specialist and CSM through yellow card system where appropriate.
8. Discontinue treatment (where necessary) on the advice of the specialist.

## Referral Criteria

1. Patients will have received at least 3 months of midodrine therapy on hospital prescription.
2. Patients will have been stabilised on a suitable dose of midodrine.
3. The specialist will have carried out an assessment of efficacy

## Licensed Indications

Bramox ( Midodrine ) 2.5mg and 5mg tablets are licensed for use in adults for the treatment of severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate. Use for treatment of syncope or orthostatic hypotension unrelated to autonomic dysfunction is not covered by the product license and is classed as unlicensed use.

## Recommended Dosage and Administration

Initial dose: 2.5 mg three times a day (Bramox 2.5 mg tablets are also available). 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.
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.
The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension.
There is limited data on dosing in the elderly and there are no specific studies which have focused on a possible dose reduction in the elderly population. Cautious dose titration is recommended.

## Background Pharmacology

Midodrine is a peripheral α-adrenergic agonist that is almost completely absorbed after oral administration and undergoes enzymatic hydrolysis to form its pharmacologically active metabolite, desglymidodrine.
Desglymidodrine is a sympathomimetic agent with a direct and selective effect on the peripheral α1-adrenergic receptors. This α1-stimulative effect induces vasoconstriction of the venous system (causing a reduction in venous pooling). The α1-adrenergic effects of desglymidodrine are almost wholly attributable to the (-) enantiomer of desglymidodrine. After taking midodrine, which is a racemic mixture, (+) desglymidodrine is also present, though this contributes almost nothing to the desired effect.

## Adverse Effects

For further information on adverse effects please refer to to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

Common or very common

flushing, gastrointestinal discomfort, headache, nausea, paraesthesia, piloerection (goosebumps), postural hypertension ( dose – dependent), pruritus of the scalp, skin reactions, stomatitis, urinary disorders,

Uncommon

Sleep disorders, anxiety, arrhythmias, irritability.

Rare or very rare

abnormal hepatic function and raised liver enzymes, palpitations.

Frequency not known

confusion, vomiting, diarrhoea.

## Drug Interactions

For detailed information on drug interactions, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk
Below is a summary of some of the key 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 with other specific α-adrenergic agonists, the effect of midodrine is blocked by α-adrenergic antagonists such as 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.

**Glycosides**

Simultaneous use of digitalis preparations 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 or glucocorticoids (e.g. fludrocortisone) may be at increased risk of glaucoma/increased intraocular pressure, and should be carefully monitored.

## Precautions and Contraindications

For further information on contraindications and cautions in use, please refer to the online BNF which can be accessed via
https://bnf.nice.org.uk/
or from the Summary of Product Characteristics which can be accessed via:
www.medicines.org.uk

## Contraindications

• Severe organic heart disease (e.g. bradycardia, myocardial infarction, 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.

**Pregnancy**

Manufacture advises avoid – toxicity from animal studies.

**Conception and contraception**

Manufacturer recommends effective contraception during treatment in women of child bearing potential.

**Breastfeeding**

Manufacturer advises avoid- no information available.

**Special warnings – precautions in use**

**Severe orthostatic hypotension with supine hypertension**

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 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 dose should be taken at least four hours before bedtime (see dose and administration page 4)

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, further treatment with midodrine should be stopped.

**Atherosclerotic cardiovascular 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. Use of the drug may cause urinary retention.

**Elderly patients**

Manufacture recommends cautious dose titration.

**Renal and hepatic function**

**Manufacture advises avoid in severe or acute impairment.**

**Heart rate**

Slowing of the heart rate 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. Patients should be monitored for signs or symptoms suggesting bradycardia.

**Paediatric population**

The safety and efficacy of midodrine in children have not been established. No data are available.

**Elderly population**

There is limited data on dosing in the elderly and there are no specific studies which have focused on a possible dose reduction in the elderly population. Cautious dose titration is recommended.

**Monitoring**

**Baseline:**

Blood pressure (supine and standing), U&E, creatinine, LFTs, .
Thereafter – Blood pressure (supine and standing) weekly for first 4 weeks and monthly thereafter. U&E/creatinine every 3 months. LFTs every 6 months or as instructed by specialist team.

**Treatment should be stopped and advice from the supervising specialist sought if:**

- The patient complains of symptoms suggestive of supine hypertension (as noted above)
- Blood pressure rises above 160/100

**Indication of Likely Cost of Therapy in Primary Care**

| | | |
|---|---|---|
| Midodrine (Bramox) 2.5mg | 100 tabs (£55.05) | 2.5mg tds for 28 days £46.24 |
| Midodrine (Bramox) 5mg | 100 tabs (£75.05) | 5mg tds for 28 days £63.04 |
| | | 10mg tds for 28 days £126.08 |

**Contact Details**

Grantham Hospital Cardiology Team
Cardiology Secretaries (01476) 464791

Lincoln County Hospital Cardiology Team
Cardiology Secretaries (0152) 573800

Pilgrim Hospital Cardiology Team
Cardiology Secretaries (01205) 445538

**References**

1. NICE evidence summary: new medicines orthostatic hypotension due to autonomic dysfunction: midodrine. October 2015.
2. Midodrine hydrochloride (Bramox®) 2.5 mg and 5 mg tablets. Enc 4 Appx 3. Reference number 2650. Accessed online 29th October 2015.
3. PACE Bulletin Vol 7 No 10 June 2013.
4. Horizon scanning Research & Intelligence Centre. Midodrine (Bramox) for orthostatic hypotension. May 2015.
5. MIMS accessed online November 2015

Update November 2018

6. PACE Bulletin Vol 12 No 9.
7. BNF online accessed November 2018
8. Summary of Product Characteristics Bramox® 2.5mg, Last updated on emc 16th Oct 2018.
9. Summary of Product Characteristics Bramox® 5mg, Last updated on emc 18th Oct 2018.

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**Approved at meeting of Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) November 16th 2018.**