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, 70,September - March 2016, p. 4)
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 guideline in this series are available from members of the Arden and GEM Commissioning Support Unit – Lincolnshire Prescribing & Medicines Optimisation Team.

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Principles of shared care

The General Medical Council published their Good Practice In Prescribing And Managing Medicines which came into effect 25th February 2013. A section of the guidance provides recommendations for the sharing of care which applies to any instance when care is shared between different services.

Good practice recommendation 35.

- Decisions about who and who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on patients best interest rather than on convenience or the cost of the medicine and associated monitoring or follow-up

Good practice recommendation 36.

- Shared care requires the agreement of all parties including the patient. Effective communication and continuing liaison between all parties to a shared care agreement is essential.

Good practice recommendation 37.

- If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

Good practice recommendation 38.

- If you delegate assessment of a patients' suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required

Good practice recommendation 39.

- In both cases, you will be responsible for any prescription you sign.

Good practice recommendation 40.

- If you recommend that a colleague, for example a junior doctor or general practitioner, prescribes a particular medicine for a patient, you must consider their competence to do so. You must satisfy yourself that they have sufficient knowledge of the patient and the medicine, experience (especially in the case of junior doctors) and information to prescribe. You should be willing to answer their questions and otherwise assist them in caring for the patient, as required

Good practice recommendation 41

- If you share responsibility for a patient's care with a colleague, you must be competent to exercise your share of clinical responsibility.

You should:

a) Keep yourself informed about the medicines that are to be prescribed for the patient
b) Be able to recognise serious and frequently occurring adverse side effects

c) Make sure appropriate clinical monitoring arrangements are in place and that the patient and the healthcare professionals involved understand them

d) Keep up to date with relevance guidance on the use of the medicines and on the management of the patient's condition

Good practice recommendation 42

- In proposing a shared care arrangement, specialists may advise the patient's general practitioner which medicine to prescribe. If you are recommending a new or rarely prescribed medicine you should specify the dosage and means of administration and agree a protocol for treatment. You should explain the use of unlicensed medicines and departures from authoritative guidance or recommended treatments and provide both the general practitioner and the patient with sufficient information to permit the safe management of the patient's condition.

Good practice recommendation 43

- If you are uncertain about your competence to take responsibility for the patients continuing care you should seek further information or advice from the clinician with whom the patient's care is shared or from another experienced colleague. If you are still not satisfied you should explain this to the other clinician and to the patient and make appropriate arrangements for their continuing care.

Drug Details

Approved Name: **Midodrine**
Brand Name: Bramox
Form and Strength: Tablets 2.5mg and 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.

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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

Most commonly reported adverse effects are: piloerection (goosebumps),pruritus of the scalp and dysuria.
Commonly reported adverse effects are paraesthesia, paraesthesia of the scalp ,headache, supine hypertension (dose dependent effect), nausea, dyspepsia, stomatitis, pruritus,chills,flushing, rash and urinary retention
Uncommon adverse effects are: Sleep disorders, insomnia, restlessness,excitability Irritability, reflex,bradycardia, and urinary urgency
Rare adverse effects are: tachycardia,palpitations and abnormal hepatic function and raised liver enzymes.
Frequency not known (cannot be estimated from available data) : Anxiety, confusional state, abdominal pain, vomiting, diarrhoea.

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 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.

Potential pharmacokinetic interactions

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.

Precautions and Contraindications

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.

Pregnancy

There are no data from the use of midodrine hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses. Bramox 5 mg tablets are not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

It is unknown whether midodrine and its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Bramox 5 mg tablets should not be used during breastfeeding.

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 physican. 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.

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 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..
Renal and hepatic function
Use is contraindicated in patients with acute renal impairment or severe renal impairment. There are no specific studies that have focused on a possible dose reduction in patients with renal impairment Treatment with midodrine has not been studied in patients with hepatic impairment. It is therefore recommended to evaluate the renal and hepatic parameters before starting treatment with midodrine and on a regular basis
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

Information Given to the Patient

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Contact Details

References

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