East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine and proposed indication	Orthostatic hypotension due to autonomic dysfunction: midodrine
Requested by	Ashford & St Peter's Hospital NHS Foundation Trust

SUMMARY

Background

Currently midodrine is red on the traffic light system with a policy statement being issued in Nov 2012 http://pad.res360.net/Content/Documents/PCN%2038-2012%20Midodrine%20for%20Orthostatic%20Hypotension.pdf
Since then midodrine (Bramox) is the first medicine to receive a UK marketing authorisation for orthostatic hypotension being launched in the UK in July 2015. It is indicated only for people with orthostatic hypotension due to autonomic dysfunction: use for other types of orthostatic hypotension is off-label. Following the availability of a licensed product the PCN have received requests to review the current policy statement and traffic light status.

Clinical Effectiveness

Information taken from **NICE esnm61** – full document attached
2 RCTs (Low et al. 1997 and Jankovic et al. 1993) found that midodrine 10 mg 3 times daily increased standing blood pressure statistically significantly more than placebo, 1 hour after the dose was taken.
Improvements in patient- and investigator-rated symptoms were seen with midodrine compared with placebo in both RCTs. However, the symptom measurement scales were not reported to have been validated.

Safety

Information taken from **NICE esnm61** – full document attached
According to the summary of product characteristics, the most common adverse effects of midodrine are piloerection, pruritus of the scalp and dysuria, occurring in more than 1 in 10 people.
Adverse effects occurring in between 1 in 10 and 1 in 100 people include paraesthesia, headache, nausea, dyspepsia, stomatitis, pruritus, rash, chills, flushing, urinary retention and supine hypertension.

Patient factors

Information taken from **NICE esnm61** – full document attached
No published evidence is available for outcomes such as quality of life, falls or ability to carry out daily activities.
Because of the risk of supine hypertension, regular monitoring of supine and standing blood pressure is necessary. 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 adverse effects by their doctor (see summary of product characteristics).

Cost implications

Information taken from **NICE esnm61** – full document attached
Midodrine 5 mg (Bramox) costs £75.05 per 100 tablets excluding VAT (MIMS, August 2015). Therefore, 28 days' supply at a maintenance dosage of 10 mg 3 times daily costs £126.08 excluding VAT.
The cost of the licensed product is lower than that of unlicensed products used in 2014 (NHS prescription cost analysis for England 2014).
The manufacturer of Bramox, Brancaster Pharma Limited, considers that up to around 3500 people in the UK may be eligible for midodrine treatment under the terms of the marketing authorisation.

Relevant guidance / reviews
NICE esnm61: Orthostatic hypotension due to autonomic dysfunction: midodrine Oct 2015
Likely place in therapy relative to current treatments
The European Federation of Neurological Societies advises that, rather than achieving a target blood pressure, goals of treatment for orthostatic hypotension are improving functional capacity and quality of life, and preventing injury. More evidence from well-designed RCTs is needed assessing midodrine for orthostatic hypotension on outcomes such as these, over periods of more than 4 weeks. The European Federation of Neurological Societies currently recommends fludrocortisone as the usual first-line pharmacological treatment option for orthostatic hypotension. Their guidance was updated in 2011 and, at that time, midodrine was considered a second-line option, alone or in combination with, for example, fludrocortisone. Midodrine (Bramox) is now licensed for treating a limited cohort of adults with severe orthostatic hypotension due to autonomic dysfunction in whom corrective factors have been ruled out and other forms of treatment are inadequate. Other forms of treatment recommended by the European Federation of Neurological Societies are physical measures including compression stockings, carefully controlled and individualised exercise training, blood pressure monitoring and increased water and salt ingestion. The summary of product characteristics does not define severe orthostatic hypotension because assessment of severity is subjective, based on symptoms and the impact of the condition on the person's lifestyle and quality of life. Midodrine is commonly associated with adverse effects, which can sometimes be serious (for example, supine hypertension), and it seems sensible to consider a trial of the drug only when other options have been tried and the patient's quality of life remains adversely affected by the condition. As highlighted in the summary of product characteristics, a careful evaluation of the response to treatment and of the overall balance of the expected benefits and risks should be undertaken with the person before any dose increase or advice to continue therapy for long periods. Local decision makers need to take safety, efficacy, patient factors and cost into account when considering the likely place in therapy of midodrine for orthostatic hypotension caused by autonomic dysfunction.
Recommendation to PCN
That midodrine (Bramox) should be considered as amber on the traffic light system for the treatment of patients with severe orthostatic hypotension for whom corrective factors have been ruled out and other forms of treatment are inadequate (other forms of treatment recommended by the European Federation of Neurological Societies are physical measures including compression stockings, carefully controlled and individualised exercise training, blood pressure monitoring and increased water and salt ingestion). Midodrine (Bramox) should be considered as an alternative first-line pharmacological treatment option for orthostatic hypotension alongside fludrocortisone.

Medicine details	
Name and brand name	Midodrine (Bramox®)
Licensed indication, formulation and usual dosage	Orthostatic hypotension may be idiopathic or may arise as a result of disorders affecting the autonomic nervous system (for example, Parkinson's disease, multiple system atrophy or diabetic autonomic neuropathy), from a loss of blood volume or dehydration, or because of certain medications such as antihypertensive drugs. Bramox® is licensed only for treating adults with severe orthostatic hypotension due to autonomic dysfunction when corrective factors have

	been ruled out and other forms of treatment are inadequate. Use for other types of orthostatic hypotension is off-label. Bramox® is available as 2.5mg and 5mg tablets. 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.
Brief description of disease **Summary of mechanism of action, and relevant pharmacokinetics**	On standing, gravity causes blood to pool in the lower extremities. The autonomic nervous system usually counteracts this by increasing heart rate, cardiac contractility and vascular tone, and skeletal muscle in the lower body contracts to prevent excessive pooling (Freeman et al. 2011). Orthostatic (or postural) hypotension results from an inadequate physiological response to postural changes in blood pressure. In people with the condition, standing leads to an abnormally large drop in blood pressure, which can result in symptoms such as light-headedness, dizziness, blurring of vision, syncope (fainting) and falls (Lahrmann et al. 2011). Symptoms resolve as blood pressure returns to normal (for example, on returning to a seated position). The definition of orthostatic hypotension endorsed by the European Federation of Autonomic Societies is a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing, or of tilting the body (with the head up) to at least a 60° angle on a tilt table (Freeman et al. 2011). Midodrine is a pro-drug of desglymidodrine. Desglymidodrine is a sympathomimetic that acts on peripheral alpha adrenergic receptors, causing vasoconstriction of the venous system and increased peripheral arterial resistance, resulting in an increase in blood pressure. Midodrine is not associated with effects on the central nervous system. See the summary of product characteristics for more information.
Important drug interactions	See SPC for full list **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.
Monitoring requirements	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. 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.
Other considerations	**Contraindications include (see SPC for full list)** Hypertension. Severe renal impairment (creatinine clearance of less than 30ml/min). Urinary retention. Hyperthyroidism Narrow angle glaucoma.

Potential patient group (if appropriate to include)	
Potential patient numbers per 100,000	The manufacturer of Bramox, Brancaster Pharma Limited, considers that up to around 3500 people in the UK may be eligible for midodrine treatment under the terms of the marketing authorisation.
Outcomes required	The European Federation of Neurological Societies advises that, rather than achieving a target blood pressure, goals of treatment for orthostatic hypotension are improving functional capacity and quality of life, and preventing injury

Evidence review
See attached **NICE esnm61**

Health economic considerations	
Cost per year per patient	According to the NHS prescription cost analysis for England 2014, in that year, the cost of midodrine 5 mg was between £1.27 and £1.66 per tablet and the cost of midodrine 2.5 mg was between £1.84 and £2.21 per tablet. The acquisition cost of the licensed midodrine product is lower (Bramox, £0.75 per 5 mg tablet and £0.55 per 2.5 mg tablet; MIMS, August 2015). 28 days' supply at a maintenance dosage of 10 mg 3 times daily costs £126.08 excluding VAT.
Alternative treatments cost per patient per year	Non-pharmacological management options are recommended first-line (including compression stockings, blood pressure monitoring and increased water and salt ingestion) Fludrocortisone (Florinef) is licensed in the UK for partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for treating salt-losing adrenogenital syndrome. It does not have marketing authorisation in the UK for treating orthostatic hypotension; therefore, use for this indication is off-label. The European Federation of Neurological Societies recommends that the dosage of fludrocortisone should be 100−200 micrograms/day for orthostatic hypotension (Lahrmann et al. 2011). The cost of this dosage is between £1.41 and £2.83 for 28 days' supply excluding VAT (Drug Tariff, September 2015).

	Update In April 2016 100 tablets of fludrocortisone 100mcg cost £5.05 (ie 5p a tablet) In May 2016 30 tablets of fludrocortisone 100mcg cost £30 (ie £1 a tablet) The cost of 100-200mcg/day of fludrocortisone based on May 2016 tariff price is between £28 and £56 for 28 days' supply excluding VAT Midodrine and fludrocortisone may be used as combination therapy.

References

Freeman R, Wieling W, Axelrod FB et al. (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clinical Autonomic Research 21: 69–72

Lahrmann P, Cortelli P, Hilz M et al. (2011) Orthostatic hypotension. In: Gilbus NE, Barnes MP, Brainin M, editors. European handbook of neurological management. Volume 1. Oxford: Blackwell, 469−76

NICE esnm61 Oct 2015 (accessed 12th April 2016)

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