

# Orthostatic hypotension due to autonomic dysfunction: midodrine

## Evidence summary

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[nice.org.uk/guidance/esnm61](https://www.nice.org.uk/guidance/esnm61)

This advice replaces ESUOM5.

## Key points from the evidence

The content of this evidence summary was up-to-date in October 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Two randomised controlled trials (RCTs) (n=171 and n=97) found that midodrine significantly increased standing blood pressure 1 hour post-dose compared with placebo in people with symptomatic orthostatic hypotension due to autonomic dysfunction. There was also limited evidence that midodrine improved some symptoms of orthostatic hypotension, such as syncope (fainting) and low energy levels. However, results for other symptoms such as light-headedness and dizziness were less positive, and the studies did not assess quality of life, falls or ability to carry out daily activities.

Adverse events seen more commonly with midodrine than with placebo in the RCTs included piloerection (goose bumps), itching and tingling of the scalp, urinary retention and increased blood

pressure when lying down (supine hypertension). These adverse events sometimes led to discontinuation of treatment.

**Regulatory status:** Midodrine ([Bramox](#)) is the first medicine to receive a UK marketing authorisation for orthostatic hypotension. It is indicated only for people with orthostatic hypotension due to autonomic dysfunction: use for other types of orthostatic hypotension is off-label.

Effectiveness	Safety
<ul style="list-style-type: none"><li>• 2 RCTs (<a href="#">Low et al. 1997</a> and <a href="#">Jankovic et al. 1993</a>) found that midodrine 10 mg 3 times daily increased standing blood pressure statistically significantly more than placebo, 1 hour after the dose was taken.</li><li>• 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.</li></ul>	<ul style="list-style-type: none"><li>• According to the <a href="#">summary of product characteristics</a>, the most common adverse effects of midodrine are piloerection, pruritus of the scalp and dysuria, occurring in more than 1 in 10 people.</li><li>• 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.</li></ul>

Patient factors	Resource implications
<ul style="list-style-type: none"> <li>No published evidence is available for outcomes such as quality of life, falls or ability to carry out daily activities.</li> <li>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 <a href="#">summary of product characteristics</a>).</li> </ul>	<ul style="list-style-type: none"> <li>Midodrine 5 mg (<a href="#">Bramox</a>) costs £75.05 per 100 tablets excluding VAT (<a href="#">MIMS</a>, August 2015). Therefore, 28 days' supply at a maintenance dosage of 10 mg 3 times daily costs £126.08 excluding VAT.</li> <li>The cost of the licensed product is lower than that of unlicensed products used in 2014 (<a href="#">NHS prescription cost analysis for England 2014</a>).</li> <li>The manufacturer of <a href="#">Bramox</a>, 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.</li> </ul>

## Introduction and current guidance

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 and falls.

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.

The [European Federation of Neurological Societies](#) recommends individually tailored therapy for orthostatic hypotension. 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. Use of both of these medicines was 'off-label' for orthostatic hypotension when the guidance was updated in 2011.

Midodrine ([Bramox](#)) is now licensed for orthostatic hypotension due to autonomic dysfunction: use for other types of orthostatic hypotension is off-label. Use of fludrocortisone ([Florinef](#)) for treating any type of orthostatic hypotension is still off-label (see the [NICE evidence summary: unlicensed off-label medicine on fludrocortisone for orthostatic hypotension](#) for more information). In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using midodrine or fludrocortisone outside their authorised indications.

[Full text of introduction and current guidance.](#)

## Product overview

Midodrine ([Bramox](#), Brancaster Pharma Limited) received a marketing authorisation in March 2015 and was launched in the UK in July 2015. It is licensed 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.

Bramox is a branded generic and licensing was based on a bioequivalence study demonstrating equivalence to the European product, Gutron.

[Full text of product overview.](#)

## Evidence review

- This evidence review is primarily based on 2 RCTs ([Low et al. 1997](#), n=171 and [Jankovic et al. 1993](#), n=97) that compared midodrine (2.5–10 mg 3 times daily) with placebo over 3–4 weeks in people with symptomatic orthostatic hypotension caused by autonomic dysfunction.
- [Low et al. \(1997\)](#) found that midodrine 10 mg 3 times daily increased standing systolic blood pressure statistically significantly more than placebo 1 hour after receiving the dose during all 3 weeks of treatment (change after midodrine dose: between +19.5 mmHg and +22.4 mmHg; change after placebo dose: between –1.3 mmHg and +2.8 mmHg;  $p < 0.01$  for midodrine compared with placebo in all 3 weeks).
- [Jankovic et al. \(1993\)](#) found that, after 4 weeks, the average change in pre- to post-dose standing systolic blood pressure was statistically significantly higher with midodrine 10 mg 3 times daily (+22 mmHg, a 23% increase) than with placebo (+3 mmHg, a 3% increase;  $p < 0.001$ ).

- In [Low et al. \(1997\)](#), statistically significantly less light-headedness was seen with midodrine 10 mg 3 times daily than with placebo at week 2 of the treatment period ( $p=0.02$ ). This difference was not statistically significant at weeks 1 or 3. Patient- and investigator-rated improvements in global orthostatic symptoms were statistically significantly greater with midodrine than with placebo after 3 weeks of treatment ( $p=0.03$  and  $p<0.001$  respectively).
- In [Jankovic et al. \(1993\)](#), there was no statistically significant improvement in the percentage of patients reporting improvement from baseline with any dose of midodrine (2.5 mg, 5 mg or 10 mg 3 times daily) for dizziness, weakness or fatigue, blurred vision or ability to stand for over 15 minutes, compared with placebo. At all doses studied, midodrine statistically significantly increased the proportion of patients reporting improvement in syncope compared with placebo ( $p<0.05$ ), with the greatest improvement seen with 10 mg 3 times daily ( $p<0.001$ ).
- Dropout from the study by [Low et al. \(1997\)](#) was higher in the midodrine arm (23/82, 28.0%) than in the placebo arm (9/89, 10.1%; based on figures reported as not completing the trial; statistical comparison not reported). In the midodrine group, 3 people dropped out because of pilomotor reactions, 7 for urinary urgency or retention, 5 for supine hypertension, and 8 for other reasons. In [Jankovic et al. \(1993\)](#), 5/74 patients taking midodrine (6.8%, mainly due to supine hypertension) and 3/104 taking placebo (2.9%) discontinued because of adverse effects.
- The most common adverse effects related to midodrine therapy (occurring in more than 1 in 10 people) are piloerection, pruritus of the scalp and dysuria, which lead to discontinuation of treatment in some people. Patients should be monitored for supine hypertension, which occurs in between 1 in 10 and 1 in 100 people. Reducing the dose of midodrine may resolve supine hypertension but, if it does not, treatment must be stopped. See the [summary of product characteristics](#) for more information.
- The main limitation of the 2 RCTs is the focus on disease-oriented outcomes (changes in standing blood pressure), as opposed to patient-oriented outcomes such as quality of life, falls or ability to carry out daily activities. Symptoms were assessed in the studies but any validity assessment of the measurement scales used was not reported, and data on patient-reported symptoms recorded at follow-up appointments may be subject to recall bias. In addition, it is unclear whether any statistically significant differences in symptoms between midodrine and placebo were [clinically important](#). Both studies compared midodrine with placebo, possibly because other pharmacological treatment options for orthostatic hypotension are limited making studies with an active comparator difficult. The studies were also of short duration meaning the long-term efficacy and safety of midodrine is unclear.

- Three systematic reviews and meta-analyses have considered midodrine for orthostatic hypotension ([Ong et al. 2013](#), [Parsaik et al. 2013](#) and [Izcovich et al. 2014](#)). They included studies in various types of orthostatic hypotension, although the results are largely driven by the 2 RCTs in orthostatic hypotension due to autonomic dysfunction that are the focus of this evidence summary. Overall, the systematic reviews and meta-analyses concluded that the quality of the evidence supporting the use of midodrine in orthostatic hypotension is limited by the lack of robust clinical data.

[Full text of evidence review.](#)

## Context

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.

[Full text of context.](#)

## *Estimated impact for the NHS*

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).

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.

[Full text of estimated impact for the NHS.](#)

### **About this evidence summary**

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

## **Full evidence summary**

### *Introduction and current guidance*

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).

Not all people with orthostatic hypotension experience symptoms. In addition, people who present with an injury or a fall may not be able to recall symptoms before the fall, meaning that the presence of orthostatic hypotension might be missed unless actively sought as part of a structured assessment. This is particularly the case in people aged over 65 years ([Petkar S et al. 2006](#)).

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](#)).

Orthostatic hypotension may be idiopathic (Bradbury–Eggleston syndrome) 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 ([Gibbons et al. 2010](#)).

Orthostatic hypotension is more common in older people, and estimates of prevalence range from 5% to 30% of people aged over 65 years (in the general population), up to 60% of people with Parkinson's disease, and up to 70% of people living in care homes ([Freeman et al. 2011](#); [Lahrmann et al. 2011](#)). It is estimated that about 0.2% of people aged over 75 years are admitted to hospital with problems relating to orthostatic hypotension ([Gibbons et al. 2010](#)).

NICE guidance on [transient loss of consciousness in adults and young people](#) advises that, if orthostatic hypotension is suspected after an initial assessment, when the history is typical and there are no features suggesting an alternative diagnosis, then the person should have their blood pressure measured lying and standing (with repeated measurements while standing for 3 minutes). The guidance advises that if orthostatic hypotension is confirmed, the likely causes should be considered and the condition should be managed appropriately. The NICE clinical guideline on [Parkinson's disease](#) (currently being [updated](#)) recommends that people with Parkinson's disease should have orthostatic hypotension treated appropriately. Specific management options are not discussed in these guidelines.

The European Federation of Neurological Societies' guideline recommends individually tailored therapy for orthostatic hypotension ([Lahrmann et al. 2011](#)) and advises that goals of treatment are improving functional capacity and quality of life, and preventing injury, rather than achieving a target blood pressure. Note that this considers orthostatic hypotension generally, not just orthostatic hypotension due to autonomic dysfunction. Recommended management options are:



- Patient education on orthostatic hypertension and advice on factors that influence blood pressure (for example, high environmental temperatures, sudden changes in posture, alcohol, and large, carbohydrate-rich meals).
- Physical measures including raising the head of the bed, moving to upright gradually, leg crossing, bending or squatting, elastic stockings and abdominal compression bands.
- Carefully controlled and individualised exercise training (swimming, aerobics, cycling and walking).
- Blood pressure monitoring and management of raised blood pressure when lying down (supine hypertension), if needed.
- Increased water and salt ingestion.
- Pharmacological treatment, with fludrocortisone first-line (see the [NICE evidence summary: unlicensed off-label medicine on fludrocortisone for orthostatic hypotension](#)). Midodrine is recommended as a second-line option, alone or in combination with, for example, fludrocortisone. Other pharmacological options that may be considered include ephedrine, pyridostigmine and subcutaneous octreotide. Note that the guideline was last updated in 2011 and does not consider marketing authorisations for individual medicines.

The [European Society of Cardiology guidelines on the diagnosis and management of syncope](#) include a section on orthostatic hypotension, which makes similar recommendations.

This evidence summary considers midodrine, the first medicine to receive a UK marketing authorisation for orthostatic hypotension (due to autonomic dysfunction).

## *Product overview*

### **Drug action**

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.

## Licensed therapeutic indication

Midodrine ([Bramox](#), Brancaster Pharma Limited) received a marketing authorisation in March 2015 and was launched in the UK in July 2015. It is licensed 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.

Bramox is a branded generic and licensing was based on a bioequivalence study demonstrating equivalence to the European product, Gutron.

## Course and cost

According to the [summary of product characteristics](#), midodrine should be initiated at a dosage of 2.5 mg 3 times daily. The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension.

Depending on supine and standing blood pressure measurements, the dosage may be increased weekly up to a maintenance dose of 10 mg 3 times daily. 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. If supine hypertension occurs, which is not overcome by reducing the dose, treatment with midodrine must be stopped.

Midodrine 5 mg 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. Midodrine 2.5 mg costs £55.05 per 100 tablets excluding VAT.

## Evidence review

This evidence review is primarily based on 2 [randomised controlled trials](#) (RCTs) comparing midodrine with placebo for orthostatic hypertension. Three [systematic reviews](#) and [meta-analyses](#) are also outlined briefly, and an [observational study](#) provides longer-term information on the safety and tolerability of midodrine. Small ( $n < 25$ ), single-dose and open-label studies are not included in the evidence review, nor are studies that have not been published in a peer reviewed journal.

### [Low et al. \(1997\)](#)

- **Design:** This was a multicentre, randomised, 3-week, double-[blind](#), parallel-group study, with a 1-week single-blind run-in period and a 2-week washout period.

- **Patients:** It randomised 171 adults with symptomatic orthostatic hypotension (postural reduction in blood pressure of 15 mmHg or more) that was due to underlying disease associated with dysfunction of the central or peripheral adrenergic pathways. A quarter of participants had multiple system atrophy (formerly Shy–Drager syndrome), 23% had pure autonomic failure (Bradbury–Eggleston syndrome), 23% had diabetes mellitus, 12% had Parkinson's disease and 18% had other conditions. People with sustained supine hypertension (blood pressure 180/110 mmHg or more) were excluded, as were people with significant systemic illness or those already taking drugs with similar mechanisms of action to midodrine (for example, vasoactive or sympathomimetic drugs). The mean age of participants was approximately 59.5 years and half were male.
- **Comparator:** Participants were randomised to receive midodrine 10 mg or placebo 3 times a day for 3 weeks. It is unclear whether allocation was concealed. Participants could be receiving concomitant treatment with fludrocortisone, a high-salt diet and compression garments, but these treatments had to remain unchanged during the trial.
- **Outcomes:** The primary end points were standing blood pressure (measured before and 1 hour after the dose at each study visit) and light-headedness (assessed on a weekly basis). Patient- and investigator-rated improvement in global symptoms (including light-headedness, energy levels, and ability to stand and perform activities of daily living) was assessed as a secondary end point and rated from 0 (none) to 5 (excellent). It was not reported if either symptom scale had been validated. A total of 162 participants (94.7%) were evaluated, with 5 excluded for non-compliance with study medication and 4 for taking concomitant vasoactive medication. It was reported that some of the analyses were by intention to treat.

Jankovic et al. (1993)

- **Design:** This was a multicentre, randomised, double-blind, parallel-group study, with a 1-week single-blind run-in period.
- **Patients:** It included 97 adults with moderate to severe symptomatic orthostatic hypotension with progressive autonomic failure, with or without peripheral or central nervous system involvement, and a history of syncope or near syncope. Participants needed to have a postural reduction in systolic blood pressure of 15 mmHg or more or at least 2 symptoms of orthostatic hypotension moderately frequently. People with sustained supine hypertension (blood pressure 180/110 mmHg or more) were excluded, as were people with renal or hepatic impairment, pheochromocytoma, or severe cardiac abnormalities. People who were included in the trial had a history of orthostatic hypotension for between 6 months and 10 years. The most common diagnosis was diabetes (27.8%), followed by Parkinson's disease (22.7%), Bradbury–Eggleston syndrome (20.6%), and multiple system atrophy (18.6%), with other

diagnoses in 10.3% of participants. The average age of people in the trial was 61 years (range 22 years to 86 years) and 54.6% were male.

- **Comparator:** Participants were randomised to receive midodrine 2.5 mg, 5 mg or 10 mg or placebo 3 times a day for 4 weeks. It is unclear whether allocation was concealed. The higher doses of midodrine were reached by titration in 2.5 mg increments over 1 week (the 5 mg group) or 2 weeks (the 10 mg group). Participants could receive concomitant treatment with non-sympathomimetic drugs such as fludrocortisone, and non-drug treatments such as a high-salt diet and compression garments.
- **Outcomes:** The primary end points were standing systolic blood pressure (measured before and 1 hour after the midodrine or placebo dose at each study visit) and symptoms associated with orthostatic hypotension (for example, dizziness, syncope, weakness or fatigue and low energy level). Symptom questionnaires assessed how frequently participants had experienced specific symptoms in the past week, on a 3-point scale from 1 (often) to 3 (never). Ten people randomised (10.3%) were not included in the analyses: 3 were lost to follow-up, 2 experienced events unrelated to the study drug, 4 discontinued because of adverse effects and 1 had a protocol violation. For the blood pressure analysis component of the study, a further 12 people were excluded because they were unable to stand for the pre- or post-dose evaluations (10 people) or they had concomitant medication readjustments (2 people). This left 75 people who had blood pressure readings that were clinically evaluable. The results for 63 people (64.9%) were analysed.

**Table 1 Summary of results for midodrine 10 mg 3 times daily in [Low et al. \(1997\)](#) and [Jankovic et al. \(1993\)](#)**

Study	Midodrine (10 mg) 3 times daily	Placebo	Comparison: midodrine versus placebo
<a href="#">Low et al. 1997</a>	n=171 randomised (162 evaluable); results at 3 weeks		
Change in standing BP pre- to post-dose <sup>a</sup>	+22.4/+13.3	+6.0/+4.3	p<0.01
Change in supine BP pre- to post-dose <sup>a</sup>	+17.6/+9.4	+3.0/+2.8 <sup>b</sup>	p<0.01
Light-headedness symptom score	No significant difference between 10 mg midodrine and placebo after 3 weeks' treatment (p=0.06)		
Global patient-rated symptom score <sup>c</sup>	2.7	2.2	p=0.03

Global investigator-rated symptom score <sup>d</sup>	2.8	2.0	p<0.01
<u>Jankovic et al. 1993</u>	n=97 (26 in 10 mg midodrine group and 23 in placebo group, remainder receiving lower doses of midodrine); results given for 10 mg midodrine dose at 3 weeks <sup>d</sup>		
<b>Standing BP<sup>b</sup></b>	94/62	105/69	NR
Pre-dose	116/76	108/72	NR
Post-dose	+22/+15	+3/+3	p<0.001
Change			
<b>Supine BP<sup>b</sup></b>	161/91	138/81	NR
Pre-dose	174/96	136/81	NR
Post-dose	+13/+5	-2/0	p<0.05
Change			
% participants reporting improvement in the frequency of symptoms	Higher in the 10 mg midodrine group than in the placebo group for syncope (p<0.001), energy level (p<0.05) and feelings of depression (p<0.05)  No significant difference in dizziness, weakness or fatigue, blurred vision, or ability to stand for more than 15 minutes between 10 mg midodrine and placebo		
% participants reporting 'feeling better'	Higher in the 10 mg midodrine group than in the placebo group (p<0.05)		
Abbreviations: BP, blood pressure; NR, not reported; p, <u>p value</u> .			
<sup>a</sup> Mean systolic or diastolic blood pressure (mmHg); BP taken before and 1 hour post-dose.			
<sup>b</sup> Diastolic BP figures for placebo reported here are corrected figures reported in an <u>erratum</u> for the original paper.			
<sup>c</sup> Improvement in symptoms of light-headedness, ability to stand and orthostatic energy level in the past week rated from 0 (none) to 5 (excellent).			
<sup>d</sup> Results are reported in the table for 10 mg midodrine 3 times daily. The study also included 2.5 mg and 5 mg doses of midodrine 3 times daily and results for these arms are summarised in the text.			

## Clinical effectiveness

### *Blood pressure*

Low et al. (1997) found that standing systolic blood pressure (a primary outcome) increased statistically significantly more in the midodrine group (10 mg 3 times daily) than in the placebo group 1 hour after receiving the dose during all 3 weeks of treatment (change after midodrine dose: between +19.5 mmHg and +22.4 mmHg [21% and 24%]; change after placebo dose: between +3.5 mmHg and +6.0 mmHg [4% and 6%];  $p < 0.01$  for midodrine compared with placebo in all 3 weeks).

Supine systolic blood pressure increased statistically significantly more in the midodrine group than in the placebo group 1 hour after receiving the dose during all 3 weeks of treatment (change after midodrine dose: between +16.2 mmHg and +17.6 mmHg [11% and 12%]; change after placebo dose: between +0.0 mmHg and +3.1 mmHg [0% and 2%];  $p < 0.01$  for comparison of midodrine compared with placebo in all 3 weeks).

Standing and supine diastolic blood pressure showed a similar pattern, with statistically significantly greater increases 1 hour after a dose of midodrine than 1 hour after a dose of placebo during all 3 weeks of treatment ( $p < 0.01$  for comparison of midodrine compared with placebo in all 3 weeks).

In absolute terms, the average pre- to post-dose increase in systolic blood pressure seen with:

- midodrine was 1.9–5.6 mmHg greater when standing than when lying down
- placebo was 0.4–4.6 mmHg greater when standing than when lying down.

Jankovic et al. (1993) found that, at the end of treatment, the average change in pre- to post-dose for:

- standing systolic blood pressure (a primary outcome) was statistically significantly higher with midodrine 10 mg 3 times daily (+22 mmHg, a 23% increase) than with placebo (+3 mmHg, a 3% increase;  $p < 0.001$ )
- supine systolic blood pressure was statistically significantly higher with midodrine 10 mg 3 times daily (+13 mmHg) than with placebo (–2 mmHg;  $p < 0.05$ ).

There were similar findings for diastolic blood pressure, with post-dose change in standing and supine blood pressure being higher with midodrine 10 mg 3 times daily compared with placebo

( $p < 0.05$ ). The lower doses of midodrine did not consistently differ from placebo for measures of systolic or diastolic blood pressure.

In an analysis that only included participants with a more rigorous definition of orthostatic hypotension (marked by a postural reduction in blood pressure of 15 mmHg or more), the increase in standing systolic blood pressure in the group treated with midodrine was 31% ( $p < 0.01$ , but it is unclear whether this referred to a between-group comparison compared with placebo or a within-group comparison compared with baseline).

Overall, the percentage of post-dose responders (increase in standing systolic blood pressure of 10 mmHg or more) was higher with midodrine (47%) than with placebo (28%;  $p$  value not reported). This was also true in all of the diagnostic subgroups except for Parkinson's disease, where response rate was 69% with midodrine (11/16 participants) and 100% with placebo (3/3 participants). However, the number of people in the diagnostic subgroups was small, so the results may not be robust.

## Symptoms

In the study by [Low et al. \(1997\)](#), statistically significantly less light-headedness (the second primary outcome), including dizziness and unsteadiness) was seen with midodrine 10 mg 3 times daily than with placebo at week 2 of the treatment period ( $p = 0.02$ ). This difference was not statistically significant at weeks 1 ( $p$  value not reported) or 3 ( $p = 0.06$ ; mean light-headedness score displayed graphically; rate not reported).

[Low et al. \(1997\)](#) also found that patient- and investigator-rated improvements in global orthostatic symptoms (secondary outcomes) were statistically significantly greater with midodrine than with placebo after 3 weeks of treatment (patient mean score: 2.7 with midodrine compared with 2.2 with placebo,  $p = 0.03$ ; investigator mean score: 2.8 with midodrine compared with 2.0 with placebo,  $p < 0.001$ ).

In the study by [Jankovic et al. \(1993\)](#), there was no statistically significant improvement in the percentage of participants reporting improvement from baseline with any dose of midodrine (2.5 mg, 5 mg or 10 mg 3 times daily) for dizziness, weakness or fatigue, blurred vision or ability to stand for over 15 minutes, compared with placebo. All 3 doses of midodrine statistically significantly increased the proportion of people reporting improvement in syncope compared with placebo ( $p < 0.05$ ), with the greatest improvement seen with midodrine 10 mg 3 times daily ( $p < 0.001$ ).

For all 3 doses of midodrine, the proportion of patients who reported improvement in energy levels increased statistically significantly compared with placebo ( $p < 0.05$ ). For the 10 mg dose of midodrine, the proportion of patients who reported improvement in depression increased statistically significantly compared with placebo ( $p < 0.05$ ); the other doses of midodrine did not differ significantly from placebo.

Results were also analysed by evaluating the percentage improvement in symptom scores from baseline. This supported the improvements with midodrine 10 mg 3 times daily for syncope, energy levels and feelings of depression, but not for lower doses ( $p < 0.05$ ).

An analysis of improvement in symptom scores from baseline in people who had a 15 mmHg or more postural reduction in blood pressure at baseline found similar results. The 10 mg midodrine dose was associated with statistically significant improvements in most symptom domains, with the 5 mg and 2.5 mg doses associated with some improvements in fewer areas ( $p < 0.05$ ).

Overall, a higher proportion of participants receiving midodrine 2.5 mg or 10 mg 3 times daily reported feeling better after treatment than those receiving placebo (figures displayed graphically,  $p < 0.05$ ).

## Systematic reviews

Three systematic reviews and meta-analyses have considered midodrine for orthostatic hypotension ([Ong et al. 2013](#), [Parsaik et al. 2013](#) and [Izcovich et al. 2014](#)). The results are largely driven by the studies by [Low et al. \(1997\)](#) and [Jankovic et al. \(1993\)](#) in people with orthostatic hypotension due to autonomic dysfunction, which are the focus of this evidence summary. The majority of other studies included in the systematic reviews and meta-analyses assessed 25 people or less and were excluded from this evidence summary. One larger study ( $n=87$ ) was published in German and could not be assessed. Also, because of differences between the studies in terms of primary end points, methods of orthostatic challenge (tilt-table or standing), patient populations and definitions of orthostatic hypotension, questions have been raised over their suitability for combining in meta-analyses ([Singer et al. 2014](#)).

[Ong et al. \(2013\)](#) identified 3 RCTs that examined midodrine treatment for at least 24 hours: the 2 included in this evidence summary ([Low et al. 1997](#) and [Jankovic et al. 1993](#)) and a randomised, double-blind [cross-over study](#) comparing midodrine and ephedrine in 8 people ([Fouad-Tarazi et al. 1995](#)). The studies could not be combined in a meta-analysis because of differences in the presentation of the data and their results are discussed individually. Ong et al (2013) concluded



that there is limited good quality clinical trial evidence for the pharmacological treatment of orthostatic hypotension.

The efficacy analysis by [Parsaik et al. \(2013\)](#) included 7 RCTs (n=325): the 3 studies identified by [Ong et al. \(2013\)](#): a randomised, double-blind, placebo-controlled cross-over study looking at the effects of single doses of midodrine ([Wright et al. 1998](#), n=25), and 3 open-label studies (n=10, n=14 and n=9). Two additional open-label studies (n=16 and n=7) were included in the safety analyses.

[Parsaik et al. \(2013\)](#) (4 RCTs [2 open-label], n=129) found that changes in systolic blood pressure from supine to standing were not significantly different between midodrine and placebo. By contrast, midodrine statistically significantly improved standing systolic blood pressure change pre- and post-dose compared with placebo (4 RCTs, n=290; p<0.001). These analyses were found to be heterogeneous. A statistically significant improvement was seen with midodrine compared with placebo in patients' and investigators' global assessment of symptoms (both analyses 2 RCTs, n=185; p<0.001). Heterogeneity was seen in the patients' scale analysis. The authors concluded that the quality of the evidence is limited by imprecision, heterogeneity and increased risk of bias and there is insufficient evidence to support the use of midodrine in orthostatic hypotension. This meta-analysis was criticised by [Singer et al. \(2014\)](#).

The most recent systematic review and meta-analysis, [Izcovich et al. 2014](#), identified 6 randomised, controlled parallel group studies and randomised cross-over studies of midodrine for orthostatic hypotension. As well as the studies by Low, Jankovic, Fouad-Tarazi and Wright, these other RCTs were a study published in German ([Lachner et al. 1974](#), n=87) and a study on the clinical trials registry, [ClinicalTrials.gov \(NCT00555880\)](#), n=24).

Meta-analysis of 5 of the studies in [Izcovich et al. 2014](#) (n=406) found that symptoms of orthostatic hypotension improved in the midodrine arm compared with the placebo arm (odds ratio 3.94, 95% confidence interval [CI] 1.86 to 8.33; number needed to treat 3). No studies assessed quality of life or syncope recurrence. The authors note that confidence in this estimate is low because of moderate risk of bias in individual studies, imprecision, indirectness and publication bias.

## Safety and tolerability

### *Randomised controlled trials*

[Low et al. \(1997\)](#) found that adverse events were statistically significantly more common with midodrine than with placebo (absolute risks not reported; p=0.001). The most common adverse effects of midodrine in this RCT were:

- piloerection (goose bumps; 13% [11/82] compared with none with placebo)
- itchy scalp (10% [8/82] compared with 2% [2/89] with placebo)
- paraesthesia (pins and needles; 9% [7/82] compared with 3% [3/89] with placebo)
- paraesthesia of the scalp (9% [7/82] compared with 1% [1/89] with placebo)
- urinary retention (6% [5/82] compared with none with placebo)
- chills (5% [4/82] compared with none with placebo)
- supine hypertension (4% [3/82] compared with none with placebo)
- supine hypertension increase (2% [2/82] compared with none with placebo) and
- pruritus (2% [2/82] compared with none with placebo).

Dropout from the study by [Low et al. \(1997\)](#) was higher in the midodrine arm (23/82, 28.0%) than in the placebo arm (9/89, 10.1%; based on figures reported as not completing the trial; statistical comparison not reported). In the midodrine group, 3 people dropped out because of pilomotor reactions, 7 for urinary urgency or retention, 5 for supine hypertension, and 8 for other reasons. Some participants who withdrew from the study because of adverse effects of midodrine still wished to continue with the drug after the trial, and did so with dose titration, taking midodrine with meals, or following information on the pros and cons of treatment.

In [Jankovic et al. \(1993\)](#), the analyses of pooled safety data for the 3 midodrine groups (2.5 mg, 5 mg or 10 mg 3 times daily, n=74) and for the placebo groups included data on all 104 participants who took placebo as part of the trial. This included those who took placebo during a pre-treatment run-in week, and the 7 people who withdrew during this run-in (in some cases because of adverse effects). In this RCT, 27% of patients taking midodrine reported adverse effects compared with 22% taking placebo. The most common adverse effects with midodrine were:

- tingling or pruritus of the scalp (14% [10/74] compared with 2% [2/104] with placebo)
- supine hypertension (8% [6/74] compared with 1% [1/104] with placebo)
- urinary urgency (4% [3/74] compared with none with placebo) and
- headache (3% [2/74] compared with 1% [1/104] with placebo).

Supine hypertension was the most serious adverse effect and was considered to be related to treatment. Five people taking midodrine (5/74, 6.8%; mainly supine hypertension) and 3 taking placebo (3/104, 2.9%) discontinued because of adverse effects.

### ***Systematic reviews***

In 7 prospective studies (n=325), [Parsaik et al. \(2013\)](#) found that there was a statistically significant increase in the risk of piloerection, scalp pruritus, urinary hesitancy or retention, supine hypertension and scalp paresthesia with midodrine compared with placebo.

[Izcovich et al. 2014](#) included studies of midodrine in orthostatic hypotension and recurrent reflex syncope. In 7 studies that assessed adverse effects (n=370), the most frequent adverse effects associated with midodrine were pilomotor reactions, chills and gastrointestinal discomfort, all of which were considered to be minor. Meta-analysis of 4 of these studies (n=312) showed that the risk of adverse effects with midodrine was significantly higher than with placebo (relative risk [RR] 4.58, 95% CI 2.03 to 10.37; number needed to harm [NNH] 8). Adverse effects most frequently leading to discontinuation of treatment were supine hypertension, pilomotor reactions and urinary problems. The risk of supine hypertension was 5 times higher with midodrine compared with placebo (3 studies, n=276; RR 5.31, 95% CI 1.39 to 20.27, NNH 14).

### ***Observational study***

Limited data on longer-term safety with midodrine are available from a prospective observational study with a median follow-up of 2.7 years ([Vilches-Moraga et al. 2012](#)). A total of 135 participants aged between 64 years and 97 years (mean age 84 years) took midodrine for orthostatic hypotension (n=43) and neurocardiogenic syncope.

One hundred and one people (75%) continued midodrine until the end of the monitoring period. Most were titrated up to modest doses: 49% used 2.5 mg 3 times daily, 30% used 5 mg 3 times daily, and 18% used midodrine 7.5 mg 3 times daily. Only 3 people used 10 mg 3 times daily and 1 used 12.5 mg 3 times daily.

A total of 19 participants (14%) reported adverse drug events and 6 stopped taking midodrine because of adverse effects. Reasons for drug withdrawal included hypertension (n=3), lower urinary tract obstructive symptoms (n=1), palpitations (n=1), and nausea (n=1). Most of these developed at the starting dose of 2.5 mg of midodrine 3 times daily. All adverse drug events were recorded within the first year of treatment. All participants withdrawing from treatment did so in the first 9 months with the exception of 1 individual who stopped midodrine after 2 years as a result of midodrine-related systolic hypertension.

## **Summary of product characteristics**

According to the [summary of product characteristics](#), the most common adverse effects related to midodrine therapy 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.

Because of the risk of supine hypertension, regular monitoring of supine and standing blood pressure is necessary, for example, 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 adverse effects by their doctor.

## **Evidence strengths and limitations**

The evidence to support the use of midodrine for orthostatic hypotension due to autonomic dysfunction is based on 2 RCTs including less than 300 people ([Low et al. 1997](#) and [Jankovic et al. 1993](#)). The comparative rarity of the condition makes it difficult to conduct large, adequately [statistically powered](#) studies.

Apart from their size, the main limitation of the RCTs included in this evidence summary is the focus on disease-oriented outcomes (changes in standing blood pressure), as opposed to patient-oriented outcomes such as quality of life, falls or ability to carry out daily activities. One of the specialists involved in the production of the evidence summary noted that it is unclear how changes in blood pressure on standing (for example, the magnitude of change or the absolute low blood pressure reading) influence symptoms.

Symptoms were assessed in the RCTs but any validity assessment of the measurement scales used was not reported. In addition, it is unclear whether any statistically significant differences in symptoms between midodrine and placebo were [clinically important](#). Assessments of patient-reported symptoms at follow-up appointments may be unreliable because people may not accurately recall symptoms, particularly frail, older people. Similarly, results for self-reported syncope should be treated with caution because people with syncope may not be able to recall symptoms before the faint.

A study by [Kaufman et al. \(2012\)](#) includes results for an RCT assessing midodrine for orthostatic hypotension, including effects on activities of daily living and quality of life. However, the study by [Kaufman et al. \(2012\)](#) was designed to validate a new scale for orthostatic hypotension (the Orthostatic Hypotension Questionnaire): it is not a prospective RCT assessing midodrine. The data

on midodrine were obtained from a RCT by Shire Pharmaceuticals (n=140) and, although results are available on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00046475) (NCT00046475) and in a [letter to the US Food and Drug Administration](#) (FDA), they have not been fully published in a peer reviewed journal or by the regulator and are, therefore, not included in this evidence summary.

The limited evidence of clinical benefit of midodrine for orthostatic hypotension has been noted by the FDA. Midodrine was approved by the FDA in 1996 under its accelerated approval regulations for drugs to treat serious diseases. This form of authorisation allows the drug to be approved based on disease-oriented end points, but requires the manufacturer to confirm clinical benefit to patients after approval is granted.

In 2010, the FDA proposed [withdrawing marketing authorisation](#) for midodrine as a treatment for orthostatic hypotension because of the lack of post-marketing studies supporting its clinical efficacy in reducing symptoms. A [further update](#) stated that, although the company had conducted several clinical studies of midodrine (NCT00046475, n=140 and NCT00555880, n=24), and literature regarding the efficacy of the product has been published, the data submitted to the FDA did not verify the clinical benefit that the drug was expected to have. An FDA [memorandum](#) states that there should be adequate and well-controlled clinical trials that show statistically significant benefit for midodrine in relieving symptoms in people with orthostatic hypotension. The FDA's Center for Drug Evaluation and Research came to an [agreement with the company Shire](#) to carry out 2 further clinical trials to verify the clinical benefit of midodrine.

No further information is available on the FDA website at the time of publication of this evidence summary. However, the results of 2 studies by Shire were published on [ClinicalTrials.gov](https://clinicaltrials.gov/), in 2014:

- [Tilt-table study of the clinical efficacy of midodrine in symptomatic orthostatic hypotension](#) (NCT01518946, n=24, completed June 2013)
- [Clinical efficacy of midodrine in symptomatic orthostatic hypotension](#) (NCT01515865, n=67, completed November 2013).

These new studies have not yet been published in peer reviewed journals. In addition, midodrine is now off-patent in the USA.

As well as the focus on disease-oriented outcomes, the studies by [Low et al. \(1997\)](#) and [Jankovic et al. \(1993\)](#) have other limitations. They included relatively young people (average age about 60 years) with mixed aetiologies, all of whom had orthostatic hypotension because of autonomic failure or neurogenic causes. The results support the licensed indication for midodrine (severe orthostatic hypotension due to autonomic dysfunction) but may not apply to people with

orthostatic hypotension due to other causes, for example, older adults who have generalised vascular disease in whom use of midodrine would be off-label. Also, it is unclear whether the underlying pathology could influence the response rate because the numbers of patients in the studies were too small for robust subgroup analyses.

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 ([Lahrmann et al. 2011](#)). However, [Low et al. \(1997\)](#) and [Jankovic et al. \(1993\)](#) reported using a broader definition of orthostatic hypotension by including patients who had a decrease in blood pressure of at least 15 mmHg immediately before entering the double-blind phase.

The high level of dropouts from the midodrine group (28.0% compared with 10.1% in placebo; based on numbers with supine blood pressure assessments after 3 weeks of double-blinded treatment) in the larger of the 2 studies ([Low et al. 1997](#)) suggests that the results should be interpreted with caution because this dropout may have unbalanced the groups. Patients who dropped out may have had less improvement in symptoms.

Both of the key studies discussed in this evidence summary compared midodrine with placebo and studies using active comparators are lacking. A randomised, single-blind cross-over study ([Ramirez et al. 2014](#)) compared single doses of atomoxetine 18 mg, midodrine 5–10 mg and placebo for improving standing blood pressure and symptoms of orthostatic hypotension in 65 people with severe autonomic failure. However, [atomoxetine](#) is currently licensed for attention-deficit hyperactivity disorder: use for orthostatic hypotension is [off-label](#) and not currently recommended in treatment guidelines. The study found that atomoxetine increased standing systolic blood pressure statistically significantly more than midodrine (mean difference 7.5 mmHg, 95% CI 0.6 mmHg to 14.5 mmHg,  $p=0.03$ ). There were no significant differences between atomoxetine and midodrine in overall orthostatic hypotension-related symptoms, or in light-headedness and dizziness.

A randomised, double-blind cross-over study ([Fouad-Tarazi et al. 1995](#)) has compared midodrine and ephedrine. However, this study included only 8 people and is likely to lack statistical power.

In [Low et al. \(1997\)](#), some of the analyses were by intention to treat (including the light-headedness analysis reported in this evidence summary), but it was not clear how these analyses dealt with missing data or whether all analyses used this approach. The smaller trial ([Jankovic et al. 1993](#)) did not report using an intention-to-treat approach.

Jankovic et al. (1993) analysed multiple doses of midodrine and carried out many different statistical analyses of the results without adjusting the p value level needed for significance. This may mean that some of the statistical differences identified occurred by chance.

The improvements identified by Low et al. (1997) and Jankovic et al. (1993) in standing systolic blood pressure were seen 1 hour after the dose was taken. This may, therefore, represent the maximal effect window seen with midodrine. A previous, single-dose, cross-over RCT (Wright et al. 1998) also suggested that the increase in standing systolic blood pressure with midodrine peaked at 1 hour after the dose was taken.

The studies by Low et al. (1997) and Jankovic et al. (1993) were of short duration (4 weeks or less); therefore, the long-term efficacy and safety of midodrine are not clear. Vilches-Moraga et al. (2012) did examine both efficacy and safety prospectively over a median follow-up of 2.7 years and reported similar types of adverse events to the 2 RCTs. However, only 43/135 patients had orthostatic hypotension, and the observational nature of the study and the lack of a control group limit the interpretations that can be drawn from the study.

In Jankovic et al. (1993), safety was not reported separately for the double-blind treatment period of the study, and the placebo group included people who withdrew during an initial placebo run-in week. This may have affected the rate of adverse effects seen with placebo.

According to the summary of product characteristics, the safety and efficacy of midodrine in children have not been established. There are 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.

The studies by Low et al. (1997) and Jankovic et al. (1993) were funded by the manufacturer of midodrine at the time, the Roberts Pharmaceutical Corporation (later acquired by Shire).

## Context

### Alternative treatments

The European Federation of Neurological Societies currently recommends fludrocortisone as the usual first-line pharmacological treatment option for orthostatic hypotension. The guideline was updated in 2011 and, at that time, regarded midodrine as a second-line option, alone or in combination with, for example, fludrocortisone (Lahrmann et al. 2011).

Midodrine ([Bramox](#)) is the first medicine to receive a UK marketing authorisation for orthostatic hypotension. It is indicated only for people with orthostatic hypotension due to autonomic dysfunction: use for other types of orthostatic hypotension is off-label.

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 (see the [NICE evidence summary: unlicensed off-label medicine on fludrocortisone for orthostatic hypotension](#) for more information). In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using fludrocortisone outside its authorised indications.

## Costs of alternative treatments

No studies on the cost effectiveness of midodrine for treating orthostatic hypotension were identified.

One hundred midodrine tablets cost £55.05 for 2.5 mg and £75.05 for 5 mg. The usual maintenance dose of midodrine is 10 mg 3 times daily. The cost of this dosage using 5 mg tablets is £126.08 for 28 days' supply excluding VAT ([MIMS](#), August 2015).

The European Federation of Neurological Societies recommends that the dosage of fludrocortisone should be 100–200 micrograms/day for orthostatic hypotension ([Lahrman 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).

Midodrine and fludrocortisone may be used as combination therapy.

## *Estimated impact for the NHS*

### Likely place in therapy

Local decision makers need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of midodrine for orthostatic hypotension caused by autonomic dysfunction.

In summary, [Low et al. \(1997\)](#) and [Jankovic et al. \(1993\)](#) found that midodrine 10 mg 3 times daily increased standing blood pressure 1 hour post-dose significantly more than placebo in people with



symptomatic orthostatic hypotension due to autonomic dysfunction. There is also limited evidence that midodrine improved some symptoms of orthostatic hypotension, such as syncope and low energy levels. Results for light-headedness, dizziness and weakness or fatigue were less positive. Overall, 3 systematic reviews and meta-analyses concluded that the quality of the evidence supporting the use of midodrine in orthostatic hypotension is limited by the lack of robust clinical data ([Ong et al. 2013](#), [Parsaik et al. 2013](#) and [Izcovich et al. 2014](#)).

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 ([Lahrmann et al. 2011](#)). 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.

Midodrine ([Bramox](#)) is licensed 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. Other forms of treatment recommended by the European Federation of Neurological Societies are:

- Physical measures including raising the head of the bed, moving to upright gradually, leg crossing, bending or squatting, elastic stockings and abdominal compression bands.
- Carefully controlled and individualised exercise training (swimming, aerobics, cycling and walking).
- Blood pressure monitoring.
- Increased water and salt ingestion.

In the 2 RCTs of midodrine, patients were permitted to continue non-pharmacological treatments and fludrocortisone.

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. However, midodrine is commonly associated with adverse effects, which can sometimes be serious, 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 before any dose increase or advice to continue therapy for long periods.

The most common adverse effects related to midodrine therapy (occurring in more than 1 in 10 people) are piloerection, pruritus of the scalp and dysuria, which lead to discontinuation of treatment in some people. Patients should be monitored for supine hypertension, which occurs in between 1 in 10 and 1 in 100 people. Reducing the dose of midodrine may resolve supine hypertension but if it does not, treatment must be stopped.

Two studies are ongoing which may help to clarify midodrine's place in treating orthostatic hypotension:

- [Treatment of orthostatic hypotension in autonomic failure \(NCT00223691, estimated completion December 2016\)](#) and
- [Treatment and prognosis of neurogenic orthostatic hypotension: a prospective randomized study \(NCT02308124, estimated completion February 2016\)](#).

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).

## Estimated usage

The [NHS prescription cost analysis for England 2014](#) reports that 24,400 community prescriptions for off-label midodrine were dispensed in 2013, costing £3.5 million (net ingredient cost). The indications for these prescriptions are not available and these data do not include hospital prescriptions.

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.

## *Relevance to NICE guidance programmes*

Midodrine for orthostatic hypotension is being considered as a proposed technology appraisal via the NICE Topic Selection programme and has not yet been formally referred onto the technology appraisal work programme.

NICE guidance related to orthostatic hypotension includes:

- [Transient loss of consciousness \('blackouts'\) management in adults and young people](#) (NICE guideline CG109). This guideline includes recommendations on assessment and referral for suspected orthostatic hypotension and safety advice for people with the condition.
- [Parkinson's disease: diagnosis and management in primary and secondary care](#) (NICE guideline CG35). This guideline includes a recommendation on managing autonomic disturbances, including orthostatic hypotension. It is currently being [updated](#) (expected date of publication April 2017).
- [Falls: the assessment and prevention of falls in older people](#) (NICE guideline CG161). This guideline does not specifically refer to managing orthostatic hypotension, but is included as a related guideline because having a fall is a possible outcome of orthostatic hypotension.

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## *Development of this evidence summary*

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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## **Declarations of interest**

Both expert advisers declared no relevant interests.

### About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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