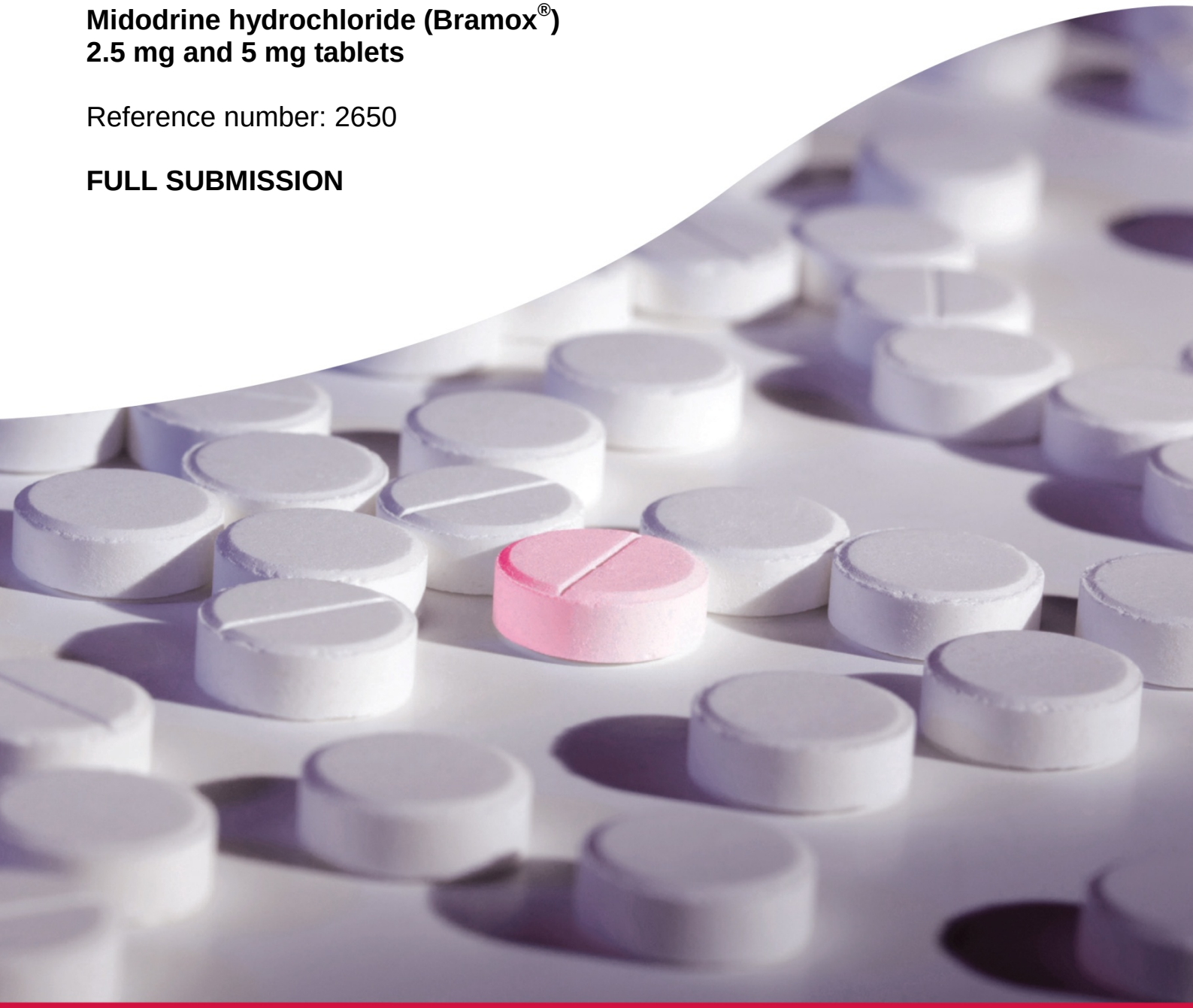
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Midodrine hydrochloride (Bramox®) 2.5 mg and 5 mg tablets

Reference number: 2650

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Midodrine hydrochloride (Bramox®) 2.5 mg and 5 mg tablets.
Reference number: 2650. September 2015.

AWMSG Secretariat Assessment Report
Midodrine hydrochloride (Bramox®) 2.5 mg and 5 mg tablets

This assessment report is based on evidence submitted by Brancaster Pharma Ltd on 24 April 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Midodrine hydrochloride (Bramox®) 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[2,3].
Dosing	The initial dose is 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 the usual maintenance dosage of 10 mg three times a day. The last daily dose should be taken at least four hours before bedtime in order to prevent supine hypertension[2,3].
Marketing authorisation date	18 March 2015[2,3].

2.0 DECISION CONTEXT

2.1 Background

The symptoms of orthostatic hypotension (or postural hypotension), an abnormal decrease in systolic blood pressure (BP) on standing are syncope (fainting), dizziness/lightheadedness, weakness or fatigue, palpitations, sweating, visual disturbances, hearing disturbances, pain in the neck and low back pain[4,5]. Orthostatic hypotension is commonly seen in the frail, elderly population whilst severe orthostatic hypotension in patients with autonomic dysfunction is rare[5–7]. Orthostatic hypotension due to autonomic dysfunction (or neurogenic orthostatic hypotension) is associated with neurological conditions e.g. Parkinson's disease, diabetic neuropathy and multiple system atrophy[7,8].

The treatment of orthostatic hypotension can be challenging and rather than aiming to achieve arbitrary BP goals; therapy should aim to improve symptoms and reduce the risk of falls and syncope[6]. Therapies used to treat orthostatic hypotension are pharmacologic e.g. fludrocortisone and ephedrine (both used off-label in the UK)[1,5,9], non-pharmacologic e.g. support garments[10], and increased water and salt intake[11]. Midodrine is the rapidly absorbed pro-drug of the pharmacologically active constituent, desglymidodrine, which induces vasoconstriction of the venous system resulting in an increase in arterial blood pressure[2]. Midodrine (ProAmantine®) was licensed for the treatment of orthostatic hypotension in the US in 1996[12]. Midodrine (Gutron®) is licensed in European countries[11](such as Germany and Italy[1,13]). Prior to the UK licensing of Bramox®, no licensed form of midodrine was available for treatment of orthostatic hypotension in Wales but unlicensed midodrine is used. [Commercial in confidence data removed].

2.2 Comparators

The comparator used in the pivotal clinical studies was placebo. The comparator included in the company's pharmacoeconomic evaluation was unlicensed midodrine[1]. It should be noted that clinical expert opinion and usage figures obtained by AWTTC

demonstrate that unlicensed midodrine is in use within NHS Wales for the indication under consideration[14].

2.3 Guidance and related advice

- National Institute for Health and Care Excellence evidence summary. ESUOM5: Postural hypotension in adults: midodrine (2013)[11].
- American Society of Hypertension. ASH position paper: evaluation and treatment of orthostatic hypotension (2013)[6].
- European Federation of Neurological Societies guidelines on the diagnosis and management of orthostatic hypotension (2006[5], updated 2011[9]).
- European Society of Cardiology. Guidelines for the diagnosis and management of syncope (version 2009)[4].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company included eight studies in the submission, two of which (Jankovic et al [1993], Low et al [1997]) were considered pivotal and are discussed in Sections 3.1 and 3.2. The remaining six studies were considered supportive and are discussed briefly in Section 3.3[1]. [Commercial in confidence data removed].

3.1 Jankovic et al.

Patients (N = 97) with moderate to severe orthostatic hypotension due to autonomic dysfunction and a mean age of 61 years were randomised (1:1:1:1) to either 2.5 mg, 5 mg or 10 mg midodrine or placebo three times per day for four weeks in a multicentred, double-blind study[1,10]. All patients included in the study demonstrated symptoms of orthostatic hypotension and the majority experienced an orthostatic BP reduction ≥ 15 mmHg (millimetres of mercury) in moving from the supine to standing position at baseline. Sympathomimetic agents (including other alpha-adrenergic agonists) were discontinued during the study but concomitant fludrocortisone, indomethacin, cardiac glycosides, compression garments, high sodium diets and electrolyte supplements were allowed to continue[1,10].

Primary end points were standing systolic BP and symptoms associated with orthostatic hypotension[1,10]. Table 1 shows that BP increase was statistically larger in the 10 mg midodrine (the usual maintenance dose[2,3]) arm versus the placebo arm. Symptoms were assessed using questionnaires in which patients (n = 63) recorded on a three point scale how often they experienced symptoms in the previous week. The symptoms included dizziness, weakness or fatigue, blurred vision, syncope, low energy levels, difficulty standing for longer than 15 minutes and depression. Syncope ($p < 0.05$), energy level ($p < 0.01$) and depression ($p < 0.05$) were significantly improved in the 10 mg arm versus placebo[10]. No significant difference in improvement between 10 mg midodrine and placebo was found for dizziness, weakness or fatigue, blurred vision or difficulty in standing. A global impression score obtained using patients' yes or no response to the statement "I feel better" was compared for 17 patients in the 10 mg midodrine arm versus 13 patients in the placebo arm. Significantly more patients receiving 10 mg midodrine than those receiving placebo reported feeling better ($p < 0.05$)[1,10].

Table 1. Blood pressure changes for midodrine versus placebo (Jankovic et al)[10].

Treatment	n	Change in standing systolic BP in mmHg (SEM)	Change in standing diastolic BP (mmHg)	Change in supine systolic BP (mmHg)	Change in supine diastolic BP (mmHg)
10 mg midodrine	21	22 (±4)	15	13	5
Placebo	18	3 (±4)	3	-2	0
p (vs placebo)		< 0.001;	< 0.05	< 0.05	< 0.05
n: number of patients completing the treatment who had BP readings which were clinically evaluable; differences in blood pressure after dosing versus before dosing (measurements taken after three or four weeks of study); SEM: standard error of the mean; mmHg: per millimetre of mercury.					

3.2 Low et al

Patients (N = 171) with orthostatic hypotension due to autonomic dysfunction and a mean age of 60 years were randomised (1:1) to either 10 mg midodrine or placebo three times per day for three weeks in a multicentred, double-blind study[1,15]. Patients included in the study had an orthostatic BP reduction of ≥ 15 mmHg and symptoms of dizziness, lightheadedness and/or unsteadiness. Concomitant treatment with fludrocortisone acetate, high salt diet and compression garments were allowed[1,15].

The two primary endpoints were standing BP and symptoms of lightheadedness (evaluated by the patients using a visual analogue scale of 0–10, where a high score equalled better outcome)[1,15]. Additionally, at the end of the treatment period, a global assessment was made by the investigator and patient separately in which patients' improvements in orthostatic symptoms (lightheadedness, ability to stand longer, energy level and ability to do daily activities living on their feet) were recorded. Standing and supine BPs were all significantly improved versus baseline for patients receiving midodrine versus those receiving placebo (see Table 2). Symptoms of lightheadedness scores were significantly higher for midodrine versus placebo-treated patients at week two of the three week treatment period (p = 0.02) but not at week three (p = 0.06). Global symptom scores shown in Table 2 were significantly favourable for midodrine patients versus those receiving placebo[1,15].

Table 2. End points for midodrine versus placebo (Low et al)[15].

	Increase in standing systolic BP (mmHg)	Increase in standing diastolic BP (mmHg)	Increase in supine systolic BP (mmHg)	Increase in supine diastolic BP (mmHg)	Global symptom score –patient rated (SD)	Global symptom score – investigator rated (SD)
Midodrine 10 mg	22.4	13.3	17.6	9.4	2.7 (0.2)	2.8 (0.2)
Placebo	6.0	4.3	3.0	6.0	2.2 (0.1)	2.0 (0.1)
p (vs placebo)	< 0.01	< 0.01	< 0.01	< 0.01	0.03	< 0.001
BP values determined on day 15 of treatment from all evaluable patients; SD: standard deviation. Global symptom scores were rated from 0 (no improvement in symptoms) to 5 (excellent improvement)						

3.3 Supportive studies

SFD246-401 (Kaufmann et al) (N = 104) was a phase IV, double blind, multicentred, randomised, placebo-controlled, cross-over study of midodrine use in patients with mild to severe orthostatic hypotension[16]. The study was seven to eight weeks in duration, with each treatment arm lasting for two weeks. Only patients who responded to midodrine in the two-week run in period were allowed to enter the study. The primary endpoint, a rating of dizziness or lightheadedness was significantly improved in favour of midodrine versus placebo (p < 0.001)[16]. Post hoc analyses showed that midodrine

performed significantly better than placebo in the “marked-severe” cohort of patients with respect to the primary efficacy variable (p=0.007).

Three smaller studies included in the submission reported a beneficial effect for midodrine with regards to an increase in standing blood pressure compared to placebo (and in one study [n=8] also to ephedrine), providing further broadly supportive evidence to the studies already discussed[17–19]. Two small tilt-table studies showed slightly longer delay to syncope for midodrine versus placebo[20,21].

3.4 [Commercial in confidence data removed].

3.5 Comparative safety

Safety data were available from the two pivotal studies and a longer term prospective, observational follow up study, Vilches-Moraga et al[22]; not all patients in this study however were relevant to the target population.

In the Low et al study adverse events were significantly more common in the midodrine arm than in the placebo arm[15]. The most common adverse events were piloerection (occurring for 11/82 patients [13%] in the midodrine arm versus 0/89 in the placebo arm) and pruritus of the scalp (for 8/82 [10%] versus 2/89 [2%]). Discontinuations in the midodrine arm (23/82 in total) were due to urinary urgency or retention (seven patients), supine hypertension (five patients), pilomotor reactions (three patients) and other reasons (eight patients)[15].

In the Jankovic et al study the data for both the midodrine arms (n = 74) and the placebo arms (n = 104) was pooled for comparison[10]. Adverse events were reported for 20/74 (27%) of patients taking midodrine and 23/104 (22%) of those taking placebo. The most common adverse events with midodrine were pruritus of the scalp 10/74 (14%) versus 2/104 (2%) for placebo and supine hypertension 6/74 (8%) versus 1/104 (1%) for placebo[10].

Vilches-Moraga et al was a prospective, observational study of patients (N = 135) treated with midodrine over 2.7 years[22]. This study however was not restricted to the indication under consideration; as only 43/135 (32%) of patients had a diagnosis of orthostatic hypotension. The majority of these patients 31/43 (72%) reported improvement of symptoms of syncope or pre-syncope compared to 12/43 (28%) who reported no improvement[22]. The number of patients discontinuing midodrine was 34/135 (25%). The reasons for discontinuation were 14/34 patients (41%) failing to maintain symptom control, 7/34 (21%) unable to keep appointments, 7/34 (21%) due to unrelated clinical deterioration and 6/34 (18%) due to adverse reaction to medicines. Side effects were reported by 19/135 (14%) of patients and six of these patients discontinued midodrine (due to hypertension [for three patients] and due to lower urinary tract symptoms [one patient], palpitations [one patient] and nausea [one patient])[22].

3.6 AWTTC critique

- Midodrine (Bramox®) is the only medicine licensed for the treatment of severe orthostatic hypotension due to autonomic dysfunction in Wales. The studies showed significant increases in standing BP and also improvement in the majority of the endpoints for patients’ symptoms for those receiving midodrine versus placebo. The Jankovic and Low studies have been considered to be adequately powered[5], however the pharmacological improvements measured for midodrine were not statistically significant for the majority of the endpoints. No studies included assessment of daily living activities.
- There is an absence of long term randomised, placebo-controlled efficacy data for midodrine; the pivotal studies had a maximum duration of three to four weeks. The applicant company highlighted that long term studies, particularly

involving the use of a placebo arm are not feasible since orthostatic hypotension tends to worsen with time[1].

- Fludrocortisone and ephedrine are both used off-label in the treatment of orthostatic hypotension ,concomitantly with midodrine[5,6]. Concomitant use of other supportive measures including fludrocortisone, high salt diet and compression garments were allowed in the midodrine studies.
- In Study FD246-401 only midodrine responders were eligible for treatment, which may have biased results in favour of midodrine. Furthermore, this study included patients with mild orthostatic hypotension, for which midodrine is not indicated[16].
- Orthostatic hypotension secondary to autonomic dysfunction is considered rare, which is reflected in the small number of patients involved in some of the supportive studies provided[6].
- The applicant company has stated that use of midodrine may help reduce the number of falls, a common and often devastating problem for older people, which leads to significant morbidity, mortality and increased use of health care services[23].
- There is a lack of long-term safety data for midodrine within its licensed indication. The Vilches-Moraga et al study provides data for 43 patients with orthostatic hypotension, but the proportion of these having severe orthostatic hypotension due to autonomic dysfunction is not provided[22].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost minimisation analysis (CMA) of midodrine (Bramox®) compared to unlicensed midodrine in patients currently being dispensed midodrine in Wales. A one year time horizon was used and no discounting was applied within the model[1]. The analysis was carried out from the perspective of the healthcare provider within Wales.

The economic analysis focused on the relative savings per patient based only on medicine costs. The company presented two analyses. In the first analysis the costs of using unlicensed midodrine were compared with the cost of using Bramox® in all patients who are currently receiving unlicensed midodrine in Wales and assumed that 40% of patients are treated in primary care versus 60% in secondary care. The second analysis used an approximate cost per patient together with an estimate of the number of patients eligible for midodrine relevant to the indication being appraised. This assumed the same split by setting (40% primary versus 60% secondary care)[1].

An alternative scenario was also explored using both the first and second analyses whereby the introduction of Bramox® (as a licensed product) results in a shift in prescribing from secondary to primary care (from 40%: 60% in the base case to 90%: 10% after the introduction of Bramox®). This scenario was provided to illustrate the impact of a shift in prescribing to primary care where the cost per tablet for unlicensed midodrine is significantly higher than in hospitals. The company justified this shift based on market research[1].

The company assumed no additional medicine administration costs or any other resources associated with the use of either licensed or unlicensed midodrine, however a list of non-medicine related costs which would be favourable to licensed versus unlicensed midodrine was provided.

Medicine acquisition costs in the first analysis for unlicensed midodrine were derived from Government Prescription Cost Analysis (PCA Wales) data (2014) for primary care

(based on prescription volume/costs for unlicensed midodrine for 2014)[24]. The cost of unlicensed midodrine in secondary care was estimated based on feedback received by the company from hospital pharmacists across the UK and using the lowest price quoted as the best estimate of the average price paid for unlicensed midodrine in hospitals in Wales. The cost of Bramox® was the currently proposed NHS list pricing from the company. Costs of treating adverse events were not included in the analyses[1].

4.1.2 Results of the company analyses

The results of the analyses are presented in Table 3. In the base case (first analysis) the company estimated that if all patients currently receiving unlicensed midodrine in Wales (company estimate:124 patients) were switched to Bramox® this would provide a total saving to NHS Wales of £57,169 per annum based on 2014 data, a cost saving of 30%.

Current purchasing agreements lead to a much higher cost for unlicensed midodrine in primary versus secondary care (approximate annual costs per patient based on a dose of two 5 mg tablets three times daily are £3,484 versus £526). Compared to unlicensed midodrine, Bramox® would have a cost of £1,643 in both primary and secondary care (costs based on dose of two 5 mg tablets taken three times daily).

The alternative scenario resulting in a shift in prescribing from secondary to primary care (10% secondary: 90% primary care) combined with the first analysis (i.e. for approximately 124 patients) would provide NHS Wales with an estimated saving of £222,388 per annum.

Table 3. Annual cost estimates of Bramox® and unlicensed midodrine with cost savings based on 2014 data[1].

Base case (first analysis approximately 124 patients[¶]; 40:60*)	**Estimated annual cost**
Bramox®	£133,284
Unlicensed midodrine	£190,453
Cost saving	£57,169
Second analysis[§] (156 patients, 40:60*)	**Estimated annual cost**
Bramox®	168,168
Unlicensed midodrine	239,460
Cost saving	71,292
Alternative scenario (first analysis approximately 124 patients[¶], 90:10[†])	**Estimated annual cost**
Bramox®	£133,284
Unlicensed midodrine	£355,672
Cost saving	£222,388
*40% primary care: 60% secondary care usage; [†] 90% primary care: 10% secondary care usage; [§]based on estimated cost per patient; [¶]back extrapolation of patient numbers by the company suggested that approximately 124 patients were prescribed unlicensed midodrine in 2014.	

In the second analysis, the company estimated the average cost per patient with unlicensed midodrine (£1,535 per annum) and Bramox® (£1,078 per annum) working backwards from the existing prescription volume/cost data and then employing assumptions of likely dosage regimens based on discussions with UK clinicians. Total costs were then calculated for 156 patients; 90% of the maximum number of patients (173) estimated by the company to be eligible for midodrine. This estimate, calculated using the existing ratio of primary to secondary care usage (40%: 60%) resulted in savings to NHS Wales of £71,292 per annum.

4.1.3 AWTTC critique

The efficacy evidence for midodrine demonstrates that it increases standing blood pressure in people with symptomatic orthostatic hypotension due to autonomic nervous system dysfunction and improves patient-rated symptoms. The CMA is based on therapeutic equivalence of Bramox® and unlicensed midodrine[1]. [Commercial in confidence data removed]. The company used a cost minimisation approach to estimate the total cost to NHS Wales of switching all patients currently receiving unlicensed midodrine to the Bramox® and also provided a second analysis in which the cost of midodrine treatment was calculated for 90% of an upper estimate of the number of indication-eligible patients in Wales. The comparator chosen for the analysis (unlicensed midodrine) seems to be appropriate as the only other therapy mainly used for this indication (fludrocortisone) might be used synergistically with midodrine. Based on evidence from clinical guidelines ephedrine might not be as effective in this setting and therefore would not be considered a suitable comparator[5,9]. The costing approach of a CMA comparing Bramox® with unlicensed midodrine is therefore considered appropriate.

Strengths of the economic evidence:

- A range of scenario analyses were included to explore assumptions around the acquisition cost of unlicensed midodrine.

Limitations of the economic evidence:

- Costs and usage volumes of unlicensed midodrine in Wales (2014) in both primary and secondary care were available to the AWTTC from NHS databases[25]. Neither the number of patients for which midodrine had been prescribed nor the indication(s) for which prescriptions had been issued were available. It was assumed that all unlicensed midodrine was prescribed for severe orthostatic hypotension due to autonomic dysfunction. Bramox® is only licensed for this rare form of orthostatic hypotension and as such the potential cost savings could therefore be smaller than those estimated in Table 3.
- The AWTTC data showed there were fewer hospital prescriptions than estimated by the company; which led to a different ratio between primary and secondary care usage and a reduced total cost. Calculations based on the total number of prescribed tablets indicated that the proportion of use in primary and secondary care was approximately 48%:52% (compared to company's estimate of 40%:60%).
- AWTTC data suggests the costs of unlicensed midodrine to be approximately £152,876 in primary care and £23,614 in secondary care (versus company estimates of £155,486 and £34,967). The total cost of unlicensed midodrine use in 2014 was therefore approximately £176,490 (versus company estimate of £190,453). Combining volumes of prescribed unlicensed midodrine from the NHS Wales databases with the company's prices for Bramox® gave a total cost of £112,334 (versus company estimate of £133,284) for substituting unlicensed midodrine with Bramox®, representing a potential saving of £64,156 (versus the company's base case saving of £57,169).
- The economic evidence presented by the company included a CMA assuming that all patients currently being prescribed unlicensed midodrine in Wales would be switching to the licensed formulation (Bramox®). A second analysis assuming that 90% of the upper estimate of the indication-eligible patients switched from unlicensed midodrine to Bramox® was also presented. This number of patients, (N = 156) is larger than the number of patients (N = 124), which the company calculated (using back-extrapolation from volumes and market feedback on dosage regimens) to be receiving midodrine in 2014.

5.0 SUMMARY OF THE EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimated the total number of patients in Wales eligible for treatment with Bramox® to be between 84 and 173[1]. In order to calculate the proportions of eligible patients in Wales the company applied estimates based on the Netherlands (which assumed a prevalence of 0.0027%) and the UK (which assumed a prevalence of 0.0056%) to the population estimates for Wales. Based on an estimated incidence of autonomic disorders which can cause orthostatic hypotension (Parkinson's disease, multiple system atrophy and diabetic neuropathy) and assuming that 10% of patients would not be controlled by "standard measures" (e.g. diet, exercise, increase salt intake, support stockings) the company estimated the total number of newly diagnosed patients each year to be 15 patients. The company used the upper estimate of the prevalence range (173 patients) and assumed an uptake of 71% in year one rising to 90% in years two to five which resulted in 123 patients being treated in year one and 156 patients each year in years two to five. The total cost estimates from the CMA (base case) were used to estimate the net budget impact for year one[1].

5.1.2 Results

Table 4 presents the budget impact estimate. The company estimated that the introduction of Bramox® would result in a saving of £56,211 per annum in year one and savings of £71,292 per annum in years two to five.

Table 4. Company-reported costs associated with the introduction of Bramox®[1].

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	173	173	173	173	173
Uptake (%)	71%	90%	90%	90%	90%
Treated patients	123	156	156	156	156
Net cost saving	£56,211	£71,292	£71,292	£71,292	£71,292

5.1.3 AWTTC critique

- The company's budget impact is based on a large increase in patient numbers (i.e. by 33 patients) in year two, but with no further increases in later years. A more realistic approach could have used the company's incidence figure of 15 extra patients added in year two with a further 15 added in subsequent years.
- Any uncertainties and limitations of the economic evidence highlighted in section 4.1.3 with regards to the acquisition costs and prescribing patterns of unlicensed midodrine also apply to the budget impact analysis.
- Due to lack of epidemiological data for orthostatic hypotension in Wales, the estimated number of patients eligible for treatment with Bramox® is based upon projections from the UK and Netherlands using assumptions and published data.

5.2 Table of comparative unit costs

Table 5 provides example comparative acquisition costs for unlicensed midodrine and Bramox®.

Table 5. Examples of treatment regimen costs.

Treatment regimen	Dose Regimen	Cost per patient per year*
Unlicensed midodrine hydrochloride	2.5 mg to 10 mg three times a day	£1,420 to £1,944
Midodrine hydrochloride (Bramox®)	2.5 mg to 10 mg three times a day	£603 to £1,644
*Costs based on prices estimated from NHS databases. This table does not imply therapeutic equivalence of the medicines and doses listed. See relevant SPCs for full dosing details[2,3].		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, the initiation and dose titration of midodrine hydrochloride (Bramox®) should be restricted to specialist prescribing and may be appropriate for prescribing within NHS Wales for the indication under consideration with a shared care agreement.

The company anticipate that midodrine hydrochloride (Bramox®) may be supplied by a home healthcare provider for some patients.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 9 June 2015
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Brancaster Pharma Ltd. Form B: Detailed appraisal submission. Midodrine hydrochloride (Bramox®). Apr 2015.

2 Brancaster Pharma Ltd. Bramox® 2.5 mg tablets. Summary of Product Characteristics. 2015. Available at: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1441947213533.pdf. Accessed Jun 2015.

3 Brancaster Pharma Ltd. Bramox® 5 mg tablets. Summary of Product Characteristics. 2015. Available at: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1441947214114.pdf. Accessed Jun 2015.

4 European Society of Cardiology. Guidelines for the diagnosis and management of syncope (version 2009). *European Heart Journal* 2009; 30: 2631-71. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3295536/. Accessed: Jun 2015.

5 Lahrmann H, Cortelli P, Hilz M et al. EFNS guidelines on the diagnosis and management of orthostatic hypotension. *Eur J Neurology* 2006; 13: 930-6. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1468-1331.2006.01512.x/epdf.

6 Shibao C, Lipsitz LA, Biaggioni I. Evaluation and treatment of orthostatic hypotension. *J Am Soc Hypertens* 2013; 7 (4): 317-24. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3769179/.

7 Figueroa JJ, Basford JR, Low PA. Preventing and treating orthostatic hypotension: as easy as A,B,C. *Cleve Clin J Med* 2010; 77 (5): 298-306. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2888469/. Accessed: Jun 2015.

8 Ha AD, Brown CH, York MK et al. The prevalence of symptomatic orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. *Parkinsonism & Related Disorders* 2011; 17 (8): 625-8. Available at: http://www.sciencedirect.com/science/article/pii/S1353802011001520. Accessed: Jun 2015.

9 Lahrmann H, Cortelli P, Hilz M et al. Orthostatic hypotension. In: Gilhus NE, Barnes MP, Brainin M, editors. *European Handbook of Neurological Management*. Blackwell; 2011.

10 Jankovic J, Gilden JL, Hiner BC et al. Neurogenic orthostatic hypotension: a double blind, placebo-controlled study with midodrine. *AJM* 1993; 95: 38-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Jancovic+Gilden+neurogenic+hypotension+midodrine+1993.

11 National Institute for Health and Care Excellence. Evidence summary, ESUOM5: Postural hypotension in adults: midodrine. Feb 2013. Available at: http://www.nice.org.uk/advice/esuom5. Accessed Jun 2015.

12 FDA. Midodrine update. 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm225444.htm. Accessed Jun 2015.

13 Drugs.com. Ingredient matches for Gutron. 2015. Available at: http://www.drugs.com/international/gutron.html. Accessed Jul 2015.

14 All Wales Therapeutics and Toxicology Centre. AWMSG appraisal FAQs, Does the All Wales Therapeutics and Toxicology Centre (AWTTC) accept unlicensed comparators? 2015. Available at: http://www.awmsg.org/awmsgonline/grabber?resId=File%2F853. Accessed Jun 2015.

15 Low PA, Gilden JL, Freeman R et al. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double blind, multicenter study. *JAMA* 1997; 277 (13): 1046-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9091692. Accessed: Jun 2015.

16 Kaufmann H, Malamut R, Norcliffe-Kaufmann L et al. The orthostatic hypotension questionaire (OHQ): validation of a novel symptom assessment scale. *Clin Auton Res* 2012; 22: 79-90. Available at:

http://link.springer.com/article/10.1007%2Fs10286-011-0146-2. Accessed: Jun 2015.
17 Fouad-Tarazi FM, Obake M, Goren H. Alpha sympathomimetic treatment of autonomic insufficiency with orthostatic hypotension. *Am J Medicine* 1995; 99: 604-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Fouad-Tarazi+1995+hypotension+ephedrine+midodrine. Accessed: Jun 2015.
18 Gilden J, Kaufmann H, Hiner B et al. Study 318. 1995. Accessed Jun 2015.
19 Wright RA, Kaufmann HC, Perera R et al. A double blind, dose response study of midodrine in neurogenic orthostatic hypotension. *Neurology* 1998; 51 (1): 120-4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/?term=Wright+midodrine+orthostatic+Perera+1998. Accessed: Jun 2015.
20 Shire Pharmaceuticals Ltd. Letter to FDA. Information package for ProAmantine® (midodrine hydrochloride). 2010. Accessed Jun 2015.
21 Shire Pharmaceuticals Ltd. Tilt-table study of the clinical efficacy of midodrine in symptomatic orthostatic hypotension. NCT01518946. 2014. Available at: https://clinicaltrials.gov/ct2/results?term=NCT01518946&Search=Search. Accessed Jun 2015.
22 Vilches-Moraga A, Paling D, Akram Q et al. Midodrine hydrochloride in the management of older adults with neurocardiogenic syncope and orthostatic hypotension: A prospective observational study. *European Geriatric Medicine* 2012; 3: 295-8. Available at: http://www.europeangeriaticmedicine.com/article/S1878-7649(12)00113-1/abstract. Accessed: Jun 2015.
23 TILDA. Fifty plus in Ireland. 2011. Available at: http://tilda.tcd.ie/assets/pdf/glossy/Tilda_Master_First_Findings_Report.pdf. Accessed Jun 2015.
24 Welsh Government. Prescriptions dispensed in the community. Prescription cost analysis: data totals 2014. Mar 2015. Available at: http://gov.wales/statistics-and-research/prescriptions-dispensed-community/?lang=en. Accessed Jun 2014.
25 NHS Wales. Prescribing costs and volumes for medicine use in Wales (CASPA and MEDUSA databases). 2015. Accessed Jun 2015.