Amber with Guidance*= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care where deemed appropriate.*

Midodrine

Background Information	Midodrine is a sympathomimetic drug with a similar chemical structure to ephedrine. It has mainly alpha-agonist properties which cause peripheral vasoconstriction, but it has no direct cardiac stimulatory effects.
BNF therapeutic class	Sympathomimetics > Vasoconstrictor
Indication	Midodrine is indicated 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.
Dosage and administration	Initial dose: 2.5 mg three times a day. Depending on the results of supine and standing blood pressure recordings, this dose may be increased weekly up to a dose of 10 mg three times a day. This is the usual maintenance dosage. A careful evaluation of the response to treatment and of the overall balance of the expected benefits and risks needs to be undertaken before any dose increase and advice to continue therapy for long periods. Administration at night should be avoided and the last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension. Midodrine may be taken with food <u>Paediatric population</u> The safety and efficacy of midodrine in children has not been established. No data available. <u>Elderly population</u> There is limited data on dosing in the elderly and there are no specific studies which have focused on a possible dose reduction in the elderly population. Cautious dose titration is recommended. <u>Patients with renal impairment</u> There are no specific studies that have focused on a possible dose reduction in patients with renal impairment. Typically, midodrine is contraindicated in patients with acute renal impairment and severe renal impairment. <u>Patients with hepatic impairment</u> There are no specific studies in this patient population. No data available.
Cautions and Contraindications	**Cautions** • **Severe orthostatic hypotension with supine hypertension: r**egular monitoring of supine and standing blood pressure is necessary due to the risk of hypertension in the supine position, e.g. at night. Patients should be told to report symptoms of supine hypertension immediately such as chest pain, palpitations, shortness of breath, headache and blurred vision, and should be monitored for these side effects by the treating physician.

Supine hypertension may often be controlled by an adjustment to the dose. If supine hypertension occurs, which is not overcome by reducing the dose, treatment with midodrine must be stopped.

The time of administration of the drug is important in this context. Avoid administration in the late evening. The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension. The risk of supine hypertension occurring during the night can be reduced by elevating the head.

- **Severe disturbances of the autonomic nervous system**: In patients suffering from a severe disturbance of the autonomic nervous system, administration of midodrine may lead to a further reduction of blood pressure when standing. If this occurs, further treatment with midodrine should be stopped.

- **Prostate disorders:** Caution is advised in patients with prostate disorders. Use of the drug may cause urinary retention.

- **Heart rate:** slowing of the heart rate may occur after midodrine administration, due to vagal reflex. Caution is advised when midodrine is used concomitantly with cardiac glycosides (such as digitalis preparations) and other agents that directly or indirectly reduce heart rate. Patients should be monitored for signs or symptoms suggesting bradycardia.

- **Atherosclerotic disease:** caution must be observed in patients with atherosclerotic disease especially with symptoms of intestinal angina or claudication of the legs.

- **Serious prostate disorder and urinary retention:** Alpha agonism may cause urinary retention and could reduce the efficacy of any treatment for BPH.

Contraindications

- Severe organic heart disease (e.g. any history of CVA/MI, bradycardia, congestive heart failure, cardiac conduction disturbances or aortic aneurysm).
- Hypertension.
- Serious obliterative blood vessel disease, cerebrovascular occlusions and vessel spasms.
- Acute kidney disease.
- Severe renal impairment (creatinine clearance of less than 30 ml/min) There is no evidence of safety/dose reductions required in this degree of renal impairment.
- Urinary retention.
- Proliferative diabetic retinopathy.
- Pheochromocytoma.
- Hyperthyroidism – monitor closely if started on midodrine.
- Narrow angle glaucoma.
- Hypersensitivity to the active substance or to any of the excipients

<u>Pregnancy</u>
No data is available for the use of midodrine hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses.

Midodrine is not recommended during pregnancy and in women of childbearing potential not using contraception.

	Breastfeeding It is unknown whether midodrine and its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Midodrine should not be used during breastfeeding. Fertility Animal studies are insufficient with respect to the assessment of fertility. Renal and Hepatic Impairment Midodrine is contraindicated in patients with acute renal impairment or severe renal impairment. Treatment with midodrine has not been studied in patients with hepatic impairment. It is therefore recommended to evaluate the renal and hepatic parameters before starting treatment with midodrine and on a regular basis. Effects on ability to drive and use machines Midodrine has negligible influence on the ability to drive and use machines. However, patients who experience dizziness or light-headedness should refrain from driving or operating machinery.
Adverse Drug Reactions	Common or very common Piloerection (goosebumps), pruritus of the scalp, dysuria, paraesthesia, paraesthesia of the scalp, headache, supine hypertension (dose dependent effect), nausea, dyspepsia, stomatitis, pruritus, chills, flushing, rash, urinary retention. Uncommon Sleep disorders, insomnia, restlessness, excitability, irritability, reflex bradycardia, urinary urgency. Rare Tachycardia, palpitations, abnormal hepatic function, raised liver enzymes. Frequency not known (cannot be estimated from available data) Anxiety, confusional state, abdominal pain, vomiting diarrhoea.
Monitoring	The only monitoring routinely required whilst on midodrine is blood pressure, to make sure that the dose is optimally titrated, and deterioration in control of BP should be referred back to the initiating specialist. The manufacturer advises the following monitoring: - regular monitoring of supine and standing blood pressure due to risk of hypertension in the supine position - hepatic and renal function before treatment and at regular intervals during treatment.
Interactions	Sympathomimetics and other vasopressor agents Concomitant treatment with sympathomimetics and other vasoconstrictive substances such as reserpine, guanethidine, tricyclic antidepressants, antihistamines, thyroid hormones and MAO-inhibitors, including treatments that are available without prescription, should be avoided as a pronounced increase in blood pressure may occur. Alpha-adrenergic antagonists As with other specific α-adrenergic agonists, the effect of midodrine is blocked by α-adrenergic antagonists such as prazosin and phentolamine.

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	Heart rate reducing drugs Monitoring is recommended if midodrine is combined with other drugs that directly or indirectly reduce the heart rate. Combination with medications which reduce heart rate (e.g. digoxin, beta blockers, some antipsychotic and dementia drugs) may increase the risk of reflex bradycardia. Glycosides Simultaneous use of digitalis preparations is not recommended, as the heart rate reducing effect may be potentiated by midodrine and heart block may occur. Corticosteroid preparations Midodrine may potentiate or enhance the hypertensive effects of corticosteroid preparations. Patients being treated with midodrine in combination with mineralocorticoids or glucocorticoids (e.g. fludrocortisone) may be at increased risk of glaucoma/increased intraocular pressure, and should be carefully monitored. Potential pharmacokinetic interactions The potential for pharmacokinetic interaction is limited as the metabolic pathways do not involve cytochrome P450 enzymes. However, decreased clearance of medicinal products metabolised by CYP2D6 (e.g. promethazine) has been reported. An increase incidence of akathisia has been reported when midodrine was given in combination with promethazine.

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Development Process

This guideline was developed following an AMBER-G (Amber with guidance) classification status of midodrine for the treatment of orthostatic hypotension by the Barnsley Area Prescribing Committee. This information has been subject to consultation and endorsement by the Area Prescribing Committee on 14th April 2021.

This guideline was reviewed and updated in October 2020.