VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Orthostatic hypotension is a syndrome; it may result from neurogenic and non-neurogenic causes.

Neurogenic orthostatic hypotension (NOH) is caused by disorders of the autonomic nervous system, and can be due to pure autonomic failure (central lesions such as Parkinson disease or multiple system atrophy) or to secondary failure (neuropathy such as diabetic or autoimmune neuropathies). Its presence, severity, and temporal course can be important clues in diagnosing Parkinson disease and differentiating it from other parkinsonian syndromes with a more ominous prognosis, such as multiple system atrophy and Lewy body dementia.

Non-neurogenic causes include cardiac impairment (e.g., from myocardial infarction or aortic stenosis), reduced intravascular volume (e.g., from dehydration, adrenal insufficiency), and vasodilation (e.g., from fever, systemic mastocytosis) (Figueroa, Basford and Low 2010) (Mathias and Kimber 1999).

The epidemiology, and its prognosis, depends on its specific cause, its severity, and the distribution of its autonomic and non-autonomic involvement. Midodrine is indicated 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.

Table 1 - Estimated prevalence of "OH" in different autonomic disorders (Metzler, et al. 2013).

Condition	Prevalence Rate (%)
Ageing	10-30
Diabetes type I	8.4
Diabetes type II	7.4
Parkinson’s disease	37-58
Dementia with Lewy bodies	30-50
MSA	75
PAF	100

Postural hypotension is uncommon in diabetes but can occur secondary to autonomic neuropathy. Symptoms are rare and include dizziness, weakness, blurred vision, tiredness,

and loss of consciousness. Patients with postural hypotension have intermittent symptoms over the years but rarely become severely disabled (Purewal and Watkins 1995).

Due to the restricted indication, the number of patients, in whom symptoms progress to the extent that requires the use of midodrine, is small, as stated by Purewal and Watkins above.

VI.2.2 Summary of treatment benefits

The evidence base supporting the efficacy of midodrine in its proposed indication, "The treatment of severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate", is based on randomised double-blind studies of patients with orthostatic hypotension due to autonomic neuropathy in line with the approved indication.

The neurogenic disorders in which its benefits were found were predominantly the Bradbury-Eggleston and Shy-Drager syndromes and diabetic autonomic neuropathy. The symptoms associated with these syndromes are markedly debilitating and unremitting and responsiveness to other therapy is often disappointing.

This marketing authorisation application is targeted to the more specific use in patients with "…severe orthostatic hypotension due to autonomic dysfunction". This is in accordance with the best clinical evidence and relates to a group of patients with severe and difficult to treat symptoms. The demonstrated benefit to these patients is clear and the indication is the same as the approved brand leader Gutron.

VI.2.3 Unknowns to treatment benefit

A limitation of the studies reviewed is that there has been no validated symptom scale and no scale had been developed until recently (Kaufmann, et al. 2012). Nonetheless the meaningful clinical benefit obtained in this difficult to treat and severely affected sub-group appears well established.

Its role in the much wider indication of orthostatic hypotension which is commonly caused by a variety of cardiac and metabolic disorders is not recommended.

VI.2.4 Summary of safety concerns

Risk	What is known	Preventability
A patient is not monitored for high blood pressure when they lie down and suffers from a stroke, or dies (Supine hypertension leading to stroke/death)	High blood pressure when a patient lies down is a known potential side effect from treatment with midodrine. High blood pressure when lying down can, if left unnoticed/untreated, lead to strokes and potentially death.	Midodrine should not be used in patients already with hypertension. This risk can be further reduced by the regular routine monitoring of blood pressure for patients being treated with midodrine, with the dose reduced or stopped altogether if high blood pressure when lying down starts to occur. Treatment with midodrine is also started using a low

Risk	What is known	Preventability
		dose, in order to minimise the potential for high blood pressure when lying down.
A patient with kidney disease takes midodrine and is unable to remove it from the body through their kidneys and so a toxic amount of midodrine builds up (Impaired excretion of Midodrine and metabolites (in patients with impaired renal function))	Midodrine is removed from the body mostly through the kidneys. A patient with kidney disease will not be able to remove midodrine from the body very easily, and therefore the drug will build up inside the body, which could reach toxic amounts.	Midodrine should not be used in patients with kidney disease. This risk can be further reduced by regularly monitoring a patient's kidneys throughout treatment with midodrine.
A patient who has a problem with the blood vessels in their eyes takes midodrine, which make their problem worse. (The vasoconstrictor effect of Midodrine may worsen conditions that are particularly sensitive, especially those affecting blood vessels in the eye.)	Midodrine is thought to cause blood vessels in the body to tighten, increasing the blood pressure. In patients who have a problem with the blood vessels in their eyes, taking midodrine may make this worse.	Midodrine should not be used in patients with certain problems with their eyes, particularly when the problem concerns the blood vessels in their eyes.
Midodrine may enhance the effects of hormones and other naturally occurring substances, which may be abnormal in certain conditions. (The sympathomimetic effects of Midodrine may worsen conditions that affect the sympathetic nervous system)	A patient with problems of the thyroid or adrenal glands may have abnormal levels of norepinephrine, the effect of which would be enhanced by midodrine.	Midodrine should not be used in patients with certain conditions, such as pheochromocytoma and hyperthyroidism.
A patient suffers from further lowering of blood pressure when they stand up (Worsening of orthostatic hypotension)	In certain individuals with some nervous system disorders, treatment with midodrine can cause a patient's blood pressure to fall even further when they stand up.	This risk can be reduced by routine monitoring of blood pressure and reviewing the treatment's benefit to the patient.
A patient has trouble urinating following treatment with midodrine, which makes the problem with their prostate worse (Urinary	Midodrine may cause patients' to have difficulty urinating, especially if they already suffer from a problem with their prostate.	This risk can be reduced by ensuring the doctor prescribing midodrine checks for problems with the patient's prostate, and

Risk	What is known	Preventability
retention)		ensures that the patient promptly reports any difficulties urinating. Midodrine should not be used in patients with a serious prostate disorder.
A patient takes a medicine which raises their blood pressure, while also taking midodrine (Concomitant treatment with sympathomimetics and other vasoconstrictive substances)	Both midodrine and these other medicines raise blood pressure; therefore when taken together they can increase blood pressure significantly. Very high blood pressure is undesirable as it can cause strokes.	This risk can be reduced by providing clear information to the prescribing doctor and patient regarding avoiding taking these medicines at the same time.
A patient takes a medicine which reduces their heart rate while also taking midodrine (Concomitant treatment with drugs that increase intra-ocular pressure)	This may cause undesirable effects and therefore patients who are taking midodrine and these other medicines at the same time should be monitored more closely.	This risk can be reduced by providing a clear statement for the prescribing doctor to monitor patients taking both of these medicines.
A patient takes a medicine that increases pressure in the eye while also taking midodrine (Concomitant treatment with drugs that increase intra-ocular pressure)	Taking midodrine may enhance the effect of some medicines that may cause pressure within the eye to increase. Therefore, if midodrine is taken alongside these medicines that increase pressure within the eye, they are at an increased risk of developing certain eye problems.	This risk can be reduced by providing a clear statement for the prescribing doctor to closely monitoring patients if these medicines are taken at the same time.
A patient with severe heart disease takes midodrine (Effects in severe heart disease)	The effects of midodrine in patients with severe heart disease are not fully known and so it is important that prior to treatment the patient's medical history is known to ensure that treatment with midodrine is appropriate for the patient.	Midodrine should not be used in patients with severe heart disease.
A patient who has high pressure in their eyes takes midodrine, which make their	Taking midodrine may cause pressure within the eye to increase. Therefore if taken	Midodrine should not be used in patients with high pressure in the eye (narrow

Risk	What is known	Preventability
problem worse (Effects in narrow angle glaucoma)	in patients with high pressure in the eye (narrow angle glaucoma) it is likely to make their condition worse. It is therefore important that prior to treatment the patient's medical history is known to ensure treatment with midodrine is appropriate.	angle glaucoma).
A patient who has damage to their retina in their eye caused by their diabetes takes midodrine, causing complications (Effects in proliferative diabetic retinopathy)	Taking midodrine may cause pressure within the eye to increase. Therefore if taken in patients with damage to the retina in their eye which has been caused by their diabetes (proliferative diabetic retinopathy) it may cause complications. It is therefore important that prior to treatment the patient's medical history is known to ensure treatment with midodrine is appropriate.	Midodrine should not be used in patients with damage to the retina in their eye which has been caused by their diabetes (proliferative diabetic retinopathy).
A patient is taking midodrine while trying to have a baby, is pregnant or is breastfeeding (Use in pregnancy and lactation)	Studies in animals have shown a potential risk at doses that would be, in comparison, very high in humans. However since a risk cannot be ruled out, it is therefore important that patients do not take midodrine while pregnant or are breastfeeding.	Midodrine should not be used in patients who are pregnant or breastfeeding.
A patient with a problem with their liver takes midodrine. (Use in hepatic impairment)	The effect of midodrine on patients with problems with their livers is unknown. Therefore in these patients midodrine should not be used until more information is available. The function of a patient's liver should be tested	Midodrine should not be used in patients who have a problem with their liver.

Risk	What is known	Preventability
	routinely during treatment with midodrine.	

VI.2.5 Summary of additional risk minimisation measures by safety concerns

There are no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There is no planned post authorisation development plan.

VI.2.7 Summary of changes to the risk management plan over time

Date	Version	Summary of Changes
29 JAN 2014	1.0	This is the first RMP
19 SEP 2014	2.0	This is the second RMP, following Day 70/100 questions from the RMS (NL) and CMS (UK) respectively.