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 reference medicinal product 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 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 routinely during treatment with midodrine.	Midodrine should not be used in patients who have a problem with their liver.

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.
11 FEB 2020	3.0	This is the third RMP, to support the line extension application for the 10 mg strength.

01 JUL 2020	4.0	This is the fourth RMP, to support the line extension application for the 10mg strength, updated in accordance with GVP Module V Rev.2., following questions from the RMS (NL) at Day 70.