PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Midodrine Tillomed 2.5 mg and 5 mg tablets (herein referred as Midodrine tablets):

This is a summary of the risk management plan (RMP) for Midodrine tablets. The RMP details important risks of Midodrine tablets, how these risks can be minimised, and how more information will be obtained about Midodrine tablets' risks and uncertainties (missing information).

Midodrine tablets' summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Midodrine tablets should be used.

Important new concerns or changes to the current ones will be included in updates of Midodrine tablets' RMP.

I. The medicine and what it is used for

Midodrine tablets are authorised for treating decrease in blood pressure due to change of position (sudden change, especially from supine position but also from a sitting position to a standing position) without changes in the rate of heart beat in patients with autonomous nervous system (part of the nervous system that controls involuntary body activity) disorders.

Midodrine tablets contain midodrine hydrochloride as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Midodrine tablets, together with measures to minimise such risks and the proposed studies for learning more about Midodrine tablets' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Midodrine tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Midodrine tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be

regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Midodrine tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Increased blood pressure in sleeping position and/ or excessively high blood pressure upon simultaneous use of medicines taken for blood pressure stabilisation and other medicines that constrict blood vessels (Supine hypertension and/ or excessive hypertension upon concomitant use of sympathomimetic and other vasoconstrictive agents) • Reflex slowing of heart (Reflex bradycardia)
Important potential risks	• None
Missing information	• Use in patients with liver problems (Use in patients with hepatic impairment)

II.B Summary of important risks

<u>Important identified risks</u>

Increased blood pressure in sleeping position and/ or excessively high blood pressure upon simultaneous use of medicines taken for blood pressure stabilisation and other medicines that constrict blood vessels (Supine hypertension and/ or excessive hypertension upon concomitant use of sympathomimetic and other vasoconstrictive agents)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, the most potentially serious adverse reaction associated with midodrine therapy is marked increase in blood pressure in sleeping position (supine hypertension), which, if sustained, may cause poor blood flow to brain and cell death (stroke), heart attack (myocardial infarction), congestive heart failure, kidney insufficiency or similar disorders which individually or collectively may be deadly. Symptoms of supine hypertension are more frequently detected at the start of midodrine therapy and during the titration period. Concomitant use with adreno-sympathomimetic drugs including over-the-counter remedies should be avoided. Midodrine may enhance or potentiate the possible hypertensive effect of corticosteroid preparations. Concomitant use of midodrine with tricyclic antidepressants, alpha-sympathomimetic medicines, thyroid hormones, antihistamines,

	MAO inhibitor may enhanced sympathomimetic activity (undesired high blood pressure increase).
Risk factors and risk groups	Risk groups include: • Patients with underlying neurological disorders • Patients suffering from severely fluctuating blood pressure Risk factors include: • Concomitant use with adreno-sympathomimetic drugs • Simultaneous usage of tricyclic antidepressants, alpha-sympathomimetic medicines, thyroid hormones, antihistamines, monoamine oxidase (MAO) inhibitor, corticosteroids
Risk minimisation measures	The safety information in the proposed product information is aligned to the reference medicinal products *"Midon 2.5 mg and 5 mg Tablets"* and *"Gutron 2.5 mg and 5 mg Tablets".* **Routine risk minimisation measures:** *SmPC and PL* *Legal status:* prescription only medicine **Additional risk minimisation measures:** No additional risk minimisation measures

Reflex slowing of heart (Reflex bradycardia)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, slowing of the heart rate may occur after administration of midodrine, primarily due to vagal reflex, therefore great caution should be taken when using it together with agents that directly or indirectly slow the heart rate e.g. digitalis, beta-blocker, psychopharmacologic agents (specifically tricyclic antidepressants, phenothiazines and atypical antipsychotics). The reflex bradycardia of midodrine hydrochloride may be increased by bradycardiac effect of glycosides if used concomitantly.
Risk factors and risk groups	Risk groups include: – Patients with severe heart disease e.g. bradycardia (slow heart rate) Risk factors include: – Concomitant use with other agents that directly or indirectly slow the heart rate e.g. digitalis, beta blockers, psychopharmacologic agents (specifically tricyclic

	antidepressants, phenothiazines and atypical antipsychotics)
Risk minimisation measures	The safety information in the proposed product information is aligned to the reference medicinal products *"Midon 2.5 mg and 5 mg Tablets"* and *"Gutron 2.5 mg and 5 mg Tablets".* **Routine risk minimisation measures:** *SmPC and PL* *Legal status:* prescription only medicine **Additional risk minimisation measures:** No additional risk minimisation measures

Important potential risks

None

Missing information

Use in patients with liver problems (Use in patients with hepatic impairment)	
Risk minimisation measures	The safety information in the proposed product information is aligned to the reference medicinal products *"Midon 2.5 mg and 5 mg Tablets"* and *"Gutron 2.5 mg and 5 mg Tablets".* **Routine risk minimisation measures:** *SmPC and PL* *Legal status:* prescription only medicine **Additional risk minimisation measures:** No additional risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Midodrine tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Midodrine tablets.