Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Midodrine Tillomed 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg midodrine hydrochloride.
Excipients with known effect:
Each tablet contains 0.1 mg Sunset Yellow FCF aluminium lake (E110).
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
White to off-white, round, scored tablets debossed with 'H' above the score and 'P' below the score on one side and '504' on the other side. The diameter of the tablet is 7.10 mm.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in adults in the treatment of severe orthostatic hypotension due to dysfunction of the autonomic nervous system when corrective factors have been ruled out.

4.2 Posology and method of administration

Posology:
Adults:
The usual starting dose is 2.5 mg 2-3 times daily. The dose should be increased at weekly intervals in small increments until an optimal response is obtained. Most patients are controlled at or below 30 mg daily given in divided doses. The maintenance dosage should be determined individually for each patient to achieve optimal therapeutic effect while reducing the impact of adverse reactions.
The maximum daily dose is 30 mg given in divided doses. Doses in excess of 30mg daily are not recommended. The supine and standing blood pressure should be monitored regularly during initial treatment (at least two times a week) and the use of midodrine should be stopped if supine hypertension increases excessively. Dosing of midodrine should occur during the daytime when the patient needs to be upright. A dosing schedule of 3-4 hour intervals is suggested. The last dose should be taken at least four hours before bedtime to reduce the risk of supine hypertension.
Special populations
Elderly
Although there is no evidence to suggest that dosage requirements are different in the elderly, it is recommended that the initial dose used be small and that increases in dosage be titrated against the patients' clinical condition with caution.

The administration of midodrine should be stopped and the attending physician notified immediately if the blood pressure in either position increases above 180/100 or is considered clinically significant.

Paediatric population
Not recommended for children.
Patients with renal impairment
No specific studies have been performed addressing a possible dose-reduction in patients with renal impairment. Midodrine is contraindicated in patients with acute renal disease and severe renal impairment (see section 4.3).

Patients with hepatic impairment
No specific studies have been performed in this patient population.

Method of administration:

Midodrine Tillomed 2.5 mg tablets should be taken with a sufficient amount of fluid and can be taken at meal times.

4.3 Contraindications

Midodrine Tillomed is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypertension
- Severe organic heart disease or congestive heart failure
- Thyrotoxicosis
- Phaeochromocytoma
- Acute nephritis
- Acute renal disease
- Severe renal insufficiency (creatinine clearance <30 ml/min)
- Hypertrophy of the prostate gland with residual urine volume increased
- Proliferative diabetic retinopathy
- Urinary retention
- Hyperthyroidism
- Narrow angle glaucoma
- Obliterative or spastic vessel disease (e.g. cerebrovascular occlusions and spasms)
- Vasovagal hypotension

4.4 Special warnings and precautions for use

It is essential to monitor supine and sitting blood pressures during the use of the drug. The potential for supine and sitting hypertension should be evaluated at the beginning of midodrine therapy.
Patients with diabetes mellitus who show high blood pressure levels in supine position due to underlying neurological disorders (diabetic autonomic neuropathy) may suffer from supine hypertension with midodrine tablets. Hence, special caution is recommended.
The patients should be cautioned to report symptoms of supine hypertension immediately such as cardiac awareness (chest pain, palpitations, shortness of breath), headache, blurred vision etc, and the patient should be advised to discontinue the medication immediately. Patients with a history of cerebrovascular accidents (CVA) or with known risk factors for CVA should be monitored closely.
The supine hypertension may often be controlled by an adjustment in the midodrine dosage.
Supine hypertension may also be controlled by elevation of the head.
Patients taking midodrine should avoid concomitant use of other adreno-sympathomimetic drugs including over the counter remedies (see 4.5).
Caution should be exercised in patients with mild to moderate renal impairment (creatinine clearance >30 ml/min and <90 ml/min).
Patients with persistent labile blood pressure after stabilisation on midodrine should discontinue treatment.
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 other agents that directly or indirectly slow the heart rate (see also section 4.5) e.g. digitalis, beta blockers, psychopharmacologic agents (specifically tricyclic antidepressants, phenothiazines and atypical antipsychotics). Patients experiencing any signs or symptoms suggestive of bradycardia (pulse slowing, increased dizziness, syncope, cardiac awareness) should be advised to discontinue midodrine.
The use of midodrine in patients who have an increased risk of or suffer from glaucoma / increased intra-ocular pressure or who are treated with mineralocorticoids / fludrocortisone acetate (which may increase intra-ocular pressure) should be avoided or monitored very closely.
It is always advisable to monitor the blood pressure and renal function in patients undergoing long-term treatment with midodrine.
Treatment with midodrine in patients with liver impairment has not been studied. It is therefore recommended to evaluate the hepatic parameters before starting treatment with midodrine and on a continuous basis.

4.5 Interaction with other medicinal products and other forms of interaction

Midodrine is an inhibitor of Cytochrome P450 CYP2D6 and may therefore affect the metabolism of other drugs metabolised by this isoenzyme (e.g. perphenazine, amiodarone, metoclopramide) . This may lead to increased systemic exposure and increased effects of these drugs.
<u>Sympathomimetics and other vasopressor agents</u>

The concomitant use of midodrine with vasoconstrictor, sympathomimetic pressor agents e.g. decongestants, some appetite suppressants and other drugs which cause hypertension such as methyldopa, tricyclic antidepressants, antihistamines, thyroid hormones, MAO-inhibitors including over-the-counter remedies should be avoided as this may cause excessive hypertension.
The effects of midodrine may be antagonised by α-adrenergic blocking drugs, such as prazosine and phentolamine. The concomitant use of alpha- and beta-receptor blocking agents (which reduce the heart rate and midodrine requires careful monitoring).
Glycosides
Great caution should be taken when administering midodrine tablets to patients experiencing bradycardia produced by digitalis (or other glycosides) or psychopharmaceutical drugs since midodrine may potentiate reflex bradycardia and other kinds of conduction disorders or arrhythmias.
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. Midodrine may enhance or potentiate the possible hypertensive effect of corticosteroid preparations.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of midodrine in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Midodrine is not recommended during pregnancy and in women of childbearing potential not using contraception. Any woman becoming pregnant during treatment should be withdrawn from the treatment immediately upon established pregnancy.

Breast-feeding
It is unknown whether midodrine/metabolites are excreted in breast milk. A risk to the newborns/infants cannot be excluded. Midodrine should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or light headedness while receiving Midodrine Tillomed should refrain from operating machinery.

4.8 Undesirable effects

The following frequency categories are used for the evaluation of side-effects:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1000 to < 1/100)
Rare	(≥ 1/10000 to < 1/1000)
Very rare	(< 1/10000)
Not known	frequency cannot be estimated from the available data

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Psychiatric disorders			Sleep disorders, insomnia			Anxiety, confusional state
Nervous system disorders		Paraesthesia	Headaches, restlessness, excitability, irritation	Dizziness or light headedness		
Eye disorders				Visual disturbance		Increased tear production

Cardiac disorders			Reflex bradycardia	Tachycardia,palpitations, arrhythmias, chest pain		
Vascular disorders		Supine hypertension(blood pressure above or equal to 180/110 mmHg) with daily doses above 30 mg	Supine hypertension(blood pressure above or equal to 180/110 mmHg) with daily doses up to 7.5 mg	Cerebrovascular accident		
Gastrointestinal disorders		Nausea, vomiting, stomatitis dyspepsia	Abdominal pain			Diarrhoea
Hepatobiliary disorders				Hepatic functionabnormal, raised liver enzymes		
Skin and subcutaneous tissue disorders	Piloerection	Chills, skin rash, pruritus (mainly of the scalp), flushing				
Renal and urinary disorders	Dysuria	Urinary retention	Urinary urgency			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continuous monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*

4.9 Overdose

Overdosage of midodrine produces piloerection, sensation of coldness, an urgent desire to empty the bladder, hypertension and bradycardia.
These effects can be counteracted by induced emesis and administration of alpha-sympatholytic drugs. In marked bradycardia, atropine may be given at its usual dose. In exanthema, H-1 antihistamines should be administered.
The active metabolite desglymidodrine is dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents.
ATC-Code: C01CA17
Mechanism of action
The alpha sympathomimetic drug midodrine hydrochloride is a prodrug, which is converted to its pharmacologically active metabolite desglymidodrine in various tissues.
Pharmacodynamic reactions

Desglymidodrine is a selective alpha-1-adrenoreceptor agonist. Its effect on cardiac circulation system is mainly due to increase of systolic and diastolic blood pressure. This increase in blood pressure occurs due to arterial and venous vasoconstriction. Midodrine hydrochloride triggers alpha receptors at the bladder, which in turn is connected with increase of tone at bladder exit and delayed emptying of the bladder.

5.2 Pharmacokinetic properties

Absorption
After oral administration of a dose of 2.5 mg, midodrine hydrochloride is rapidly and completely absorbed and reaches its peak plasma concentrations after approximately 20-30 minutes (C_{max} approx. 0.01 mg/l, t_{max} < 30 min). The prodrug midodrine hydrochloride is converted in different tissues (also in liver) enzymatically into its active metabolite desglymidodrine. The absolute bioavailability of midodrine hydrochloride (and desglymidodrine) amounts to 93% after oral administration.
AUC and C_{max} increase proportionally to the doses in a dosage range of 2.5 – 22.5 mg. Administration with food increases the AUC by approximately 25%, and the C_{max} decreases by approximately 30%. The pharmacokinetics of desglymidodrine is not affected.
After oral administration of a dosage of 5 – 10 mg of midodrine hydrochloride in fasting patients with orthostatic hypertension, desglymidodrine reaches its highest plasma concentration (0.027 mg/l) approx. 1h after oral administration (t_{max} = 1.1 h) and after intravenous injection within a period of 60 – 120 min.
Distribution
The distribution of midodrine in humans was not analysed.
Midodrine and desglymidodrine bind less than 30% to plasma proteins. Studies on animals show that desglymidodrine is distributed in the target organs. The distribution of midodrine in humans has not been established, it does not appear to cross the blood-brain barrier after oral administration.
Biotransformation
This medicinal product is split into its pharmacologically active metabolite desglymidodrine through enzymatic degradation in different tissues (including liver).
Elimination
Midodrine hydrochloride is quickly eliminated from plasma ($t_{1/2}$ = 0.41 – 0.49 h), and desglymidodrine is eliminated somewhat slowly ($t_{1/2}$ = 3 h).
Midodrine hydrochloride and desglymidodrine are almost completely (91%) eliminated renally within 24 hours (approx. 40 – 60% as active metabolite, 2 – 5% as non-metabolised midodrine hydrochloride, the rest as other pharmacologically inactive metabolites). The elimination of midodrine hydrochloride or desglymidodrine through faeces is negligible. After intravenous administration, 53% of applied quantity was eliminated in the first 4 hours and 47% through urine after peroral administration. The faecal elimination is 2.1%.
Special populations
To date there are no pharmacological data about midodrine or its metabolites desglymidodrine in older patients or patients with renal and/or liver function disorders.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.
Reproduction toxicity
Studies in rats and rabbits have shown embryotoxicity, but no teratogenic effects are reported.
Genotoxicity
In-vitro and *in-vivo* studies for midodrine hydrochloride did not show any indication of mutagenic or genotoxic potential.
Carcinogenicity
Increased tumour incidence in the testicular interstitial cells was observed in carcinogenicity studies. The relevance of this observation for humans is not clear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrophobic colloidal anhydrous silica
Microcrystalline cellulose
Pregelatinized starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

As packaged for sale: 2 years
For HDPE bottle after first opening: 100 days.

6.4 Special precautions for storage

For HDPE bottle pack: This medicinal product does not require any special storage condition.
For blister pack: Store below 25^0C

6.5 Nature and contents of container

Midodrine Tillomed 5 mg tablets are available in pack sizes containing 100 x 1 tablets in PVC/PVDC/Aluminium perforated unit dose blisters.
It is also available in High Density Polyethylene (HDPE) bottle pack with 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Mittelstraße 5/5a
12529 Schönefeld
Germany

8 MARKETING AUTHORISATION NUMBER

PA23169/002/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th August 2021

10 DATE OF REVISION OF THE TEXT

February 2024