SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Midotense 2.5mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of midodrine hydrochloride.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White to off-white, 7 mm round, flat tablet with scoreline on one side.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Midotense 2.5 mg tablets are 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.

4.2 Posology and method of administration

Initial dose: 2.5 mg 3 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.

The last daily dose should be taken at least 4 hours before bedtime in order to prevent supine hypertension (see also section 4.4).

Midotense 2.5 mg tablets may be taken with food (see section 5.2).

Paediatric population

The safety and efficacy of midodrine in children has not been established. No data are available.

Elderly population

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.

Patients with renal impairment

There are no specific studies that have been 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 (see section 4.3).

Patients with hepatic impairment

There are no specific studies in this patient population (see also section 4.4).

Method of administration
For oral use.

4.3 Contraindications

- Hypertension.
- Severe organic heart disease (e.g. bradycardia, heart attack, congestive heart failure, cardiac conduction disturbances or aortic aneurysm).
- Urinary retention.
- Serious obliterative blood vessel disease, cerebrovascular occlusions and vessel spasms.
- Acute kidney disease.
- Severe renal impairment (creatinine clearance of less than 30 ml/min).
- Serious prostate disorder.
- Proliferative diabetic retinopathy.
- Pheochromocytoma.
- Hyperthyroidism.
- Narrow angle glaucoma.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Severe orthostatic hypotension with supine hypertension

Regular 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 closely for these side effects by the treating doctor. 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. 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.

Atherosclerotic disease

Caution must be observed in patients with atherosclerotic disease especially with symptoms of intestinal angina or claudication of the legs.

Prostate disorders

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

Renal and hepatic function

Midodrine is contraindicated in patients with acute renal impairment or severe renal impairment (see Section 4.3). 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 continuous basis.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetics and other vasopressor agents

Concomitant treatment with sympathomimetics and other vasoconstrictive substances such as decongestants, reserpine, guanethidine, tricyclic antidepressants, antihistamines, thyroid hormones and MAO-inhibitors, including over –the-counter remedies 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.

Heart rate reducing drugs

Monitoring is recommended if midodrine is combined with other drugs that directly or indirectly reduce the heart rate.

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

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 potentiate or enhance the hypertensive effects of corticosteroid preparations

Potential pharmacokinetic interactions

The potential for pharmacokinetic interaction is limited as the metabolic pathways do not involve cytochrome P450 enzymes (see section 5.2). However, decreased clearance of medicinal products metabolised by CYP2D6 (e.g. promethazine) has been reported.

Potential effect of other drugs on midodrine

No studies to evaluate the effect of other drugs on the pharmacokinetics of midodrine or the active metabolite desglymidodrine have been conducted. In vitro data indicate that desglymidodrine is a substrate of CYP2D6. Concomitant administration of drugs that inhibit this enzyme (e.g. quinidine, paroxetine, fluoxetine and bupropion) may cause increased plasma levels of desglymidodrine with a potential risk of increased adverse events.

Potential effect of midodrine on other drugs

Midodrine is an inhibitor of CYP2D6 and may affect the metabolism of other drugs. This may be of clinical relevance for active substances that are mainly metabolized by CYP2D6, e.g. tricyclic antidepressants, beta blockers, selective serotonin reuptake inhibitors (SSRI), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-inhibitors) type B, especially if the active substance also has a narrow therapeutic index.

Falsely elevated plasma metanephrine

Patients taking midodrine may have falsely elevated plasma metanephrine as a result of analytical interference when measured by HILIC-based HPLC-MS/MS. This potential for interference should be considered in cases where patients taking midodrine require biochemical investigation for potential phaeochromocytomas and paragangliomas.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of midodrine hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses.

Midodrine tablets are 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 new-borns/infants cannot be excluded. Midodrine tablets should not be used during breastfeeding.

Fertility

Animal studies are insufficient with respect to the assessment of fertility.

4.7 Effects on ability to drive and use machines

Midodrine tablets have negligible influence on ability to drive or use machines. However, patients who experience dizziness or light-headedness while receiving midodrine tablets should refrain from driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequent and very common adverse reactions related to midodrine therapy are piloerection, pruritus of the scalp and dysuria.

Tabulated list of adverse reactions

Organ Class	**Very Common (> 1/10)**	**Common (> 1/100, < 1/10)**	**Uncommon (> 1/1,000, < 1/100)**	**Rare (> 1/10,000, < 1/1,000)**	**Frequency not known (cannot be estimated from available data)**
Psychiatric disorders			Sleep disorders Insomnia		Anxiety Confusional state

Nervous system disorders		Paraesthesia Paraesthesia of the scalp Headache	Restlessness Excitability Irritability		
Cardiac disorders			Reflex bradycardia	Tachycardia Palpitations	
Vascular disorders		Supine hypertension (dose dependent effect)			
Gastrointestinal disorders		Nausea Dyspepsia Stomatitis			Abdominal pain Vomiting Diarrhoea
Hepatobiliary disorders				Abnormal hepatic function Raised liver enzymes	
Skin and subcutaneous tissue disorders	Piloerection (goosebumps) Pruritus of the scalp	Pruritus Chills Flushing Rash			
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 continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The symptoms of overdose are the same as those described under side effects listed in section 4.8. The following in particular may occur: hypertension, piloerection (goosebumps) and feeling cold, bradycardia (reflex bradycardia) and urinary retention.

Treatment: In addition to the main general "life support" measures, induced vomiting
and the administration of an α-sympatholytic agent (e.g. nitroprusside, phentolamine,
nitrogylcerine) is recommended, based on the pharmacology of the drug.

Bradycardia and bradycardic conduction disturbances can be blocked by atropine.

The active metabolite desglymidodrine is dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac Therapy, Adrenergic and dopaminergic agents.

ATC-code: C01C A17

Midodrine is the rapidly absorbed pro-drug of the pharmacologically active constituent desglymidodrine. Desglymidodrine is a sympathomimetic agent with a
direct and selective effect on the peripheral α1-adrenergic receptors. This α1-simulative effect induces vasoconstriction of the venous system (causing a reduction
in venous pooling). The α1-adrenergic effects of desglymidodrine are almost wholly
attributable to the (-) enantiomer of desglymidodrine. After taking midodrine, which

is a racemic mixture, (+) desglymidodrine is also present, though this contributes
almost nothing to the desired effect.

Desglymidodrine increases the peripheral arterial resistance, resulting in an increase
in arterial blood pressure.

Only limited data is available on the long-term effects of taking midodrine.

Stimulation of the α-adrenergic receptors of the bladder and the ureter increases the
sphincter muscle tone.

Desglymidodrine has no β-adrenergic effects.

5.2 Pharmacokinetic properties

Absorption

After oral administration, midodrine is rapidly and almost completely absorbed. Peak plasma concentrations are reached after approximately 30 minutes. The plasma concentration of the active metabolite, desglymidodrine, peaks after about 1 hour.

AUC and Cmax increase proportionally over the dosage range of 2.5 – 22.5 mg.

Administration with food increases the AUC by approximately 25%, and the Cmax decreases by approximately 30%. The pharmacokinetics of desglymidodrine
are not affected.

Distribution

Neither midodrine nor desgylmidodrine are bound to plasma proteins to any significant extent (less than 30%). Animal studies show that desglymidodrine is distributed in target organs and diffuses poorly across the blood brain barrier. Diffusion across the placenta has been reported. It is not known whether this drug is excreted in human milk.

Metabolism

Midodrine is partially hydrolysed before absorption (in the intestines), and partially
after absorption (in plasma) by the separation of glycine, herewith generating the

active metabolite, desglymidodrine. The elimination of desglymidodrine is primarily
caused by an oxidating metabolism, followed by (partial) conjugation.

Excretion

Midodrine (8%), desglymidodrine (40%), and their degradation products (55%) are
excreted in the urine by more than 90% within 24 hours in conjugated or nonconjugated form. The plasma elimination half-life for midodrine is approximately 30 minutes, and is approximately 3 hours for desglymidodrine. Elimination of the active
(-) enantiomer of desglymidodrine is slower than the elimination of the inactive (+)
enantiomer.

5.3 Preclinical safety data

Safety Pharmacology studies and repeat-dose toxicity studies with animals did not show any indications of a safety risk for humans at therapeutic doses. Studies in the rat and rabbit show that at maternally toxic doses, midodrine is embryotoxic. There is no evidence of teratogenicity.
Midodrine is not genotoxic and after long term studies in rats (104 weeks) and mice (78 weeks), there was no evidence that midodrine was carcinogenic at dose of up to 10 mg/kg/day and up to 15 mg/kg/day, respectively, compared to a maximum patient daily dose of 30 mg (~0.5 mg/kg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Pregelatinised Starch
Magnesium Stearate
Silica colloidal anhydrous
Talc

6.2 Incompatibilities

None known

6.3 Shelf life

24 months unopened.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium / Aluminium blisters in cartons of 30, 50, 90 or 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Transdermal Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 14308/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/05/2017

10 DATE OF REVISION OF THE TEXT

14/11/2023