SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Midodrin Evolan 2.5 mg tablets
Midodrin Evolan 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of midodrine hydrochloride
Each tablet contains 5 mg of midodrine hydrochloride

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

White, flat, round tablets embossed with “2.5” 7 mm in diameter.
White, flat, round tablets embossed with “5” 10 mm in diameter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

<Invented name> is indicated in adults for the treatment of severe orthostatic hypotension due to autonomic dysfunction when other forms of treatment and corrective factors are inadequate.

4.2. Posology and method of administration

Posology

Initial dose: 2.5 mg three times a day. Depending on the individual response, the dose may be increased weekly up to a maximum dose of 10 mg three times a day.

The blood pressure should repeatedly be measured at the start of the treatment and monitored closely after each dose increase. An ambulatory 24 h blood pressure measurement can be considered to optimize the dosage schedule.

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

<Invented name> may be taken with or without food (see section 5.2).

Paediatric population

The safety and efficacy of midodrine in children have 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 focused on a possible dose reduction in patients with renal impairment. A careful dose titration is recommended. Typically, midodrine is contraindicated in patients with acute renal impairment or 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). A careful dose titration is recommended.

Method of administration

For oral use.

4.3. Contraindications

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

4.4. Special warnings and special 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 for these side effects by the treating physican. Supine hypertension may often be controlled by an adjustment of 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 in this context. 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.
Significant elevation of arterial blood pressure in supine position is a risk factor for stroke, heart attack, heart failure, renal failure or similar disorders that may be life-threatening, individually or in combination.

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 must be stopped.

Atherosclerotic disease

Midodrine has predominantly alpha agonist properties and may therefore lead to vascular contraction. Caution must therefore be observed in patients with atherosclerotic disease especially with symptoms of intestinal angina or claudication of the legs.
If symptoms of atherosclerotic disease occur, treatment with midodrine must be discontinued.

Prostate disorders

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

Renal and hepatic function

This medicinal product 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 regular basis.
Caution should be exercised in patients with mild to moderate renal impairment (creatinine clearance >30 ml / min and <90 ml / min).

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.

Patients who experience any signs or symptoms suggestive of bradycardia (slow pulse, increased dizziness, syncope, cardiac awareness) should be instructed to discontinue treatment with midodrine.

Patients taking midodrine should avoid concomitant use of other adreno-sympathomimetic drugs (see also section 4.5).

4.5. Interaction with other medicinal products and other forms of interaction

Medicinal products that may affect <Invented name>

Sympathomimetics and other vasopressor agents

Concomitant treatment with sympathomimetics and other vasoconstrictive substances such as reserpine, guanethidine, tricyclic antidepressants, antihistamines, thyroid hormones and MAO-inhibitors, including treatments that are available without prescription, should be avoided as a pronounced increase in blood pressure may occur.

Alpha-adrenergic antagonists

As with other specific alpha-adrenergic agonists, the effect of midodrine is blocked by alpha- 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.

Potential pharmacokinetic interactions
No studies on the effects of other medicinal products on the pharmacokinetics of midodrine or the active metabolite of desglymidodrine have been performed. Based on in *vitro data*, desglymidodrine is a substrate for CYP2D6. Concomitant administration of drugs that inhibit this enzyme (eg quinidine, paroxetine, fluoxetine and bupropion) may lead to increased plasma levels of desglymidodrine with an increased risk of adverse drug reactions.

Medicinal products which may be affected by <Invented name>

Glycosides

Simultaneous use of digitalis preparations is not recommended, as the heart rate reducing effect may be potentiated by midodrine and AV-block may occur.

Corticosteroid preparations

Midodrine may potentiate or enhance the hypertensive effects of 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.

Potential pharmacokinetic interactions

Midodrine is an inhibitor of cytochrome P450 CYP2D6 and may therefore affect the metabolism of other drugs. This may be of clinical relevance to substances that are mainly metabolised by CYP2D6, e.g. some of the following drug classes, tricyclic antidepressants, beta blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (including classes 1A, 1B and 1C) and monoamine oxidase inhibitors (MAOIs) type B, especially if they also have a narrow therapeutic window.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of midodrine hydrochloride in pregnant women. Animal studies are incomplete for reproduction toxicity (see section 5.3).

<Invented name> is 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 newborns/infants cannot be excluded. <Invented name> 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

<Invented name> have negligible influence on the ability to drive and use machines.
However, patients who experience dizziness or muddle-headedness 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.

In clinical trials, hypertension in supine position and urinary retention has been reported as common adverse events, while bradycardia has been reported as an uncommon adverse reaction. Hypertonia in supine position has been shown to be a risk factor for myocardial infarction and stroke in clinical trials.

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 Flushing Rash			
Renal and Urinary disorders	Dysuria	Urinary retention	Urinary urgency		
General disorders and administration site conditions		Fever chills			

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 national reporting system listed in Appendix V

4.9. Overdose

The symptoms of overdose are the same as experienced with side effects. The following in particular may occur: hypertension, piloerection (goosebumps), cold-like symptoms, bradycardia (reflex bradycardia) and urinary retention.

Treatment: In addition to the main general “life support” measures, induced vomiting and the administration of an alpha-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 agent of the pharmacologically active ingredient desglymidodrine. Desglymidodrine is a sympathomimetic agent with a direct and selective effect on the peripheral alpha-1-adrenergic receptors. This alpha-1- stimulative effect induces vasoconstriction of the venous system (causing a reduction in venous pooling). The alpha-1-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 alpha-adrenergic receptors of the bladder and the ureter increases the sphincter muscle tone.

Desglymidodrine has no beta-adrenergic effects.

5.2. Pharmacokinetic properties

<u>Absorption</u>

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

AUC and Cmax increase proportionally to the dose across a dosage range of 2.5 – 22.5 mg. Administration with food increases the AUC by approximately 25%, and the Cmax decreases by approximately 30% for midodrine. The pharmacokinetics of desglymidodrine are not affected when administrated with food.

Distribution

Neither midodrine nor desgylmidodrine are bound to plasma proteins to any significant extent (less than 30%). Animal studies show that desglymidodrine is distributed to target organs. Data is available on diffusion through the blood-brain barrier, placenta and breast 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. CYP2D6 is the most important enzyme in the metabolism of 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 forms. 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.

Special patient groups
No data available on the pharmacokinetics of patients with renal and hepatic impairment.

5.3. Preclinical safety data

Pharmacological safety studies and toxicity studies on animals showed no evidence of human safety risks following repeated dosing. Studies on animals are insufficient to determine potential reproductive toxicity.

In carcinogenicity studies in the rat, an increased tumor incidence was observed in interstitial cells in the testicle, however, the relevance of this to humans is unclear. The results of micronuclear tests in rats also show that genotoxicity of midodrine cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Microcrystalline Cellulose
Maize Starch
Magnesium Stearate
Silica, colloidal anhydrous

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

24 months.

6.4. Special precautions for storage

Store below 25°C.

6.5. Nature and content of container

PVC-PVDC/Aluminium foil blister.

2.5 mg: Packs of tablets: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 och 500 tablets.

5 mg: Packs of tablets: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 och 500 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposa and other handlingl

7. MARKETING AUTHORISATION HOLDER

Evolan Pharma AB
Box 120
182 12 Danderyd
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2017-05-12
Date of latest renewal:
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2019-02-20