SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Midodrine Hydrochloride 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of midodrine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Spotted orange, round, flat, 7.0 mm diameter tablet with a score line on one side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Midodrine Hydrochloride is 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

Posology

Initial dose: 2.5 mg three times a day (Midodrine Hydrochloride 2.5 mg tablets are also available). 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).

Midodrine Hydrochloride 5 mg tablets may be taken with 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. 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

- 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.
- 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.
- Urinary retention.
- Proliferative diabetic retinopathy.
- Pheochromocytoma.
- Hyperthyroidism.
- Narrow angle glaucoma.

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 for these side effects by the treating physician. 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 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.

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
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.

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 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 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
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
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 from the use of midodrine hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity at maternally toxic doses. Midodrine Hydrochloride 5 mg 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 newborns/infants cannot be excluded. Midodrine Hydrochloride 5 mg 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 Hydrochloride 5 mg tablets have negligible influence on the ability to drive and use machines.
However patients who experience dizziness or light-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.

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 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 experienced with side effects. 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: C01CA17

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-stimulative 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 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 C_{max} 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 C_{max} 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%). Desglymidodrine 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.

Biotransformation

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.

Elimination
Midodrine (8%), desglymidodrine (40%), and their degradation products (55%) are excreted in the urine by more than 90% within 24 hours in conjugated or non-conjugated 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.

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

Maize starch, pregelatinized
Cellulose microcrystalline
Silica, colloidal anhydrous
Talc
Magnesium stearate
Red iron oxide (E172)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/Al blisters
Pack sizes: 100 and 100x1 tablets

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novumgen Limited
20-22 Wenlock Road,
London, N1 7GU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 55863/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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