▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – VASODRINE (MIDODRINE HYDROCHLORIDE) TABLETS

1 NAME OF THE MEDICINE

Midodrine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VASODRINE tablets contain 2.5 and 5 mg of midodrine hydrochloride.For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

VASODRINE 2.5 mg tablets are white, flat, round tablets with 7 mm diameter and embossed with “2.5”.

VASODRINE 5 mg tablets are white, flat, round tablets with 10 mm diameter and embossed with “5”.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VASODRINE is indicated in adults for the treatment of severe symptomatic orthostatic hypotension due to autonomic dysfunction when exacerbating factors have been addressedand other forms of treatment remain inadequate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The initiation of midodrine should be undertaken under close medical supervision in a controlled clinical setting by a specialist with expertise in the treatment of severe orthostatichypotension.

Initial dose: 2.5 mg three times a day. Depending on the results of supine and standing bloodpressure recordings, this dose may be increased weekly up to a dose of 10 mg three times a day. This is the usual maintenance dosage, however twice daily dosing may be appropriate for some patients.

The maximum recommended dose should not exceed 30 mg daily.

A careful evaluation of the response to treatment and of the overall balance of the expectedbenefits and risks needs to be undertaken before any dose increase or advice to continue therapy for long periods. Monitoring ambulatory blood pressure over a 24 hour period is recommended.

The last daily dose should be taken at least 4 hours before bedtime in order to prevent supinehypertension.

VASODRINE 2.5 or 5 mg tablets may be taken with food (see section 5.2 PHARMACOKINETIC PROPERTIES).

Information for the patient

Patients should be advised that they may be started on a low dose and up-titrated on a weeklybasis in 2.5mg increments to a maximum of 10mg three time daily (TDS). The timing of doses is important and will be individualised to the patient, doses should not be spread evenlyover the day and midodrine should not be taken within the 4 hour interval prior to bedtime.

Midodrine can increase the urge to urinate and can lead to volume depletion and additionalfluid intake may be required.

If a dose of medication is missed, the next dose should be taken as usual and then the patient should continue taking midodrine as prescribed. A double dose should not be taken due to theincreased risk of supine hypertension.

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. A starting dose of 2.5 mg three times daily and increasing only at 2–3 monthly intervals, may be helpful in reducing adverse reactions in elderly patients.

Patients with renal impairment

There are no specific studies that have focused on a possible dose reduction in patients withrenal impairment. Midodrine is contraindicated in patients with acute renal impairment andsevere renal impairment (see section 4.3 CONTRAINDICATIONS).

Patients with hepatic impairment

There are no specific studies in this patient population (see also section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 LIST OF EXCIPIENTS.
- 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.
- Phaeochromocytoma.
- Hyperthyroidism or thyrotoxicosis.
- Narrow angle glaucoma.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USESevere orthostatic hypotension with supine hypertension

Because midodrine hydrochloride can cause marked elevation of supine blood pressure, it should only be used in patients whose lives are considerably impaired despite standard clinical care including non-pharmacologic treatment, plasma volume expansion and lifestylealterations. The use of midodrine hydrochloride in the management of symptomatic orthostatic hypotension is based primarily on a change in a surrogate endpoint of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate endpoint considered likely to correspond to clinical benefits. At present, however, clinical benefits of midodrine hydrochloride, principally improved ability to carry out activities of daily life, have not been verified.

The number “needed to harm” for supine hypertension was 8 (95% CI 3–27), I2–14%.

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 symptomsof 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 orderto 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 symptomsof 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.

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 asdigitalis preparations) and other agents that directly or indirectly reduce heart rate. Patientsshould be monitored for signs or symptoms suggesting bradycardia.

QT interval prolongation

A retrospective analysis of a large US managed care population database reported a mean QTprolongation of 15.2 ms (95% CI:1.0, 29.4 ms, n=21) for midodrine with other unspecified concomitant drugs and non-significant increase in the a mean QT interval prolongation of 21.3 ms (95% CI: -8.2, 50.7 ms, n=9) for subjects when midodrine was used as a single agent. Nonclinical experiments in dogs demonstrated a small, but significant increase in the QT interval. A few cases of Torsades de pointes, arrhythmia and ventricular arrhythmias havebeen reported in post-marketing surveillance databases. Caution is advised when using midodrine in patients who experience bradycardia, patients with congenital QT prolongation, patients taking antiarrhythmic medications or patients taking any other medications which prolong the QT interval.

Effects of long term use

There is a lack of safety data for long-term treatment with midodrine.

Use with antihypertensive agents

Midodrine should be used with caution in combination with antihypertensive medications.

Use in hepatic impairment

Treatment with midodrine has not been studied in patients with hepatic impairment. It is therefore recommended to evaluate the hepatic parameters before starting treatment with midodrine and on a regular basis.

Use in renal impairment

This medicine is contraindicated in patients with acute renal impairment or severe renal impairment (see section 4.3 CONTRAINDICTIONS). It is therefore recommended to evaluate the renal parameters before starting treatment with midodrine and on a regular basis.

Use in the elderly

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 (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Sympathomimetics and other vasopressor agents

Concomitant treatment with sympathomimetics and other vasoconstrictive substances such asreserpine, 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.

Ergot alkaloids

Combined administration of midodrine and dihydroergotamine is not recommended based onalpha receptor interactions that may diminish any desired pressor effects.

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. Similarly, midodrine may reducethe hypotensive effect of prazosin.

Heart rate reducing drugs

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

Drugs which prolong the QT interval

Caution is advised when using midodrine in patients taking antiarrhythmic medications or patients taking any other medications which prolong the QT interval as a few cases of Torsades de pointes, arrhythmia and ventricular arrhythmias have been reported in post-marketing surveillance databases (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

Antihypertensive agents

Caution is recommended when prescribing concomitant anti-hypertensive treatments. (see 4.4SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Potential pharmacokinetic interactions

The oral absorption of midodrine is facilitated by the intestinal coupled peptide transporter(PEPT1). Because PEPT1 can transport various peptide-like drugs, such as ß-lactam antibiotics and antiviral drugs, there is potential for substrate competition and altered absorption via PEPT1 mediated transport.

The 5'-O-demethylation in human liver microsomes of desglymidodrine, the active metabolite of midodrine, was catalyzed primarily by CYP 2D6. CYP 1A2 and CYP2C19 were also found to catalyse formation of the desmethyl metabolite, although the activity wasvery low. Inhibitors of CYP2D6, such as quinidine, may enhance and prolong the activity ofdesglymidodrine.

Decreased clearance of medicinal products metabolised by CYP2D6 (e.g. promethazine) hasbeen reported.

It appears possible, although there is no supporting experimental evidence, that the high renalclearance of desyglymidodrine (a base) is due to active tubular secretion by the base- secreting system also responsible for the secretion of such drugs as metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus, there may be a potential for drug-drug interactions with these drugs.

4.6 FERTILITY, PREGNANCY AND LACTATIONEffects on fertility

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

Use in pregnancy – Pregnancy Category C

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 increased therate of embryo resorption, reduced foetal body weight in rats and rabbits, and decreased foetal survival in rabbits when given in doses 13 (rat) and 7 (rabbit) times the maximum human dose based on body surface area (mg/m^2).

VASODRINE 2.5 or 5 mg tablets are not recommended during pregnancy and in women ofchildbearing potential not using contraception.

Use in lactation

It is unknown whether midodrine and its metabolites are excreted in human milk.

A risk to newborns/infants cannot be excluded. VASODRINE 2.5 or 5 mg tablets should notbe used during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

VASODRINE 2.5 or 5 mg tablets have negligible influence on the ability to drive and usemachines. However, patients who experience dizziness or light-headedness should refrainfrom driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)Clinical trial experience

The most frequent adverse effects from the Phase III clinical study (Low 1997[1]) were pilomotor reactions and supine hypertension. The midodrine group had a significantly greaterfrequency of overall adverse events than placebo (p=0.001). The most common adverse reactions of midodrine treatment resulting in discontinuation from the study were pilomotor reactions (n=3), urinary urgency or frequency (n=7) and supine hypertension (n=5).

[1] Low PA, Gilden JL, Freeman R, et al. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA 1997;277:1046-1051.

Table 1 - Summary of the most frequently occurring adverse events from the published Phase III trial (Low 1997)

Adverse events	Number (%) of subjects	
	Midodrine (n=82)	Placebo (n=89)
Piloerection	11 (13)	0 (0)
Pruritus (scalp)	8 (10)	2 (2)
Paresthesia	7 (9)	3 (3)
Paresthesia (scalp)	7 (9)	1 (1)
Urinary retention	5 (6)	0 (0)
Chills	4 (5)	0 (0)
Supine hypertension	3 (4)	0 (0)
Supine hypertension increase	2 (2)	0 (0)
Pruritus	2 (2)	0 (0)

A random-effects meta-analysis of 9 randomised controlled trials performed by (Parsaik 2013[2], n=352) showed an increased incidence of piloerection, scalp pruritis, urinary hesitancy/retention, supine hypertension and scalp paresthesia was observed in patients receiving midodrine with pooled risk ratios of 10.53, 6.45, 5.85, 6.38 and 8.28, respectively,compared to placebo.

A second meta-analysis of 11 randomised controlled trials (The Izcovich 2014[3], n=593) meta-analysis described the most frequently reported adverse effects as pilomotor reactions described as pruritus/tingling of the scalp, goose bumps, “prickly feeling,” paraesthesia or piloerection, as well as chills and abdominal discomfort. Izcovich 2014 calculated a risk ratiofor minor side effects to occur in midodrine-patients at 4.58 (95% CI 2.03–10.37) compared to placebo. The most frequent side effects that led to a discontinuation of midodrine were supine hypertension, pilomotor reactions, and urinary problems (urinary retention, hesitancy or urgency). The increased risk of supine hypertension in midodrine-treated patients compared to placebo was calculated as a risk ratio of 5.31 (95% CI 1.39–20.27, risk difference 7% [95% CI 2–11%].

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.

[2] Parsaik AK, Singh B, Altayar O, et al. Midodrine for orthostatic hypotension: a systematic review and meta-analysis of clinical trials. J Gen Intern Med. 2013;28(11):1496-1503.

[3] Izcovich A, González Malla C, Manzotti M, et al. Midodrine for orthostatic hypotension and recurrent reflex syncope: A systematic review. Neurology 2014;83:1170-1177.

Table 2 - 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**
Psychiatric disorders			Sleep disorders Insomnia		Anxiety Confusional state
Nervous system disorders		Paraesthesia Paraesthesia of the scalp Headache	Restlessness Excitability Irritability Feeling of pressure/fullness in the head	Dizziness	
Cardiac disorders			Reflex bradycardia	Tachycardia Palpitations Asthenia	
Vascular disorders		Supine Hypertension (dose dependent effect)			Peripheral ischemia
Gastrointestinal disorders		Nausea Dyspepsia Stomatitis	Dry mouth		Abdominal pain Vomiting Diarrhea
Hepatobiliary disorders				Abnormal hepatic function Raised liver enzymes	
Skin and subcutaneous tissue disorders	Piloerection (goosebumps) Pruritus of the scalp	Pruritus Chills Flushing Rash		Erythema multiforme Dry skin Canker sore	
Renal and Urinary disorders	Dysuria	Urinary retention Urinary urgency			
Eye Disorders				Visual Field defect	
Musculoskeletal and connective tissue disorders				Backache Leg cramps	

Post Marketing Data

The following adverse events have also been reported with the use of midodrine:

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1 000, <1/100); rare (>1/10 000, < 1/1 000); very rare (<1/10000)

Psychiatric disorders:

Uncommon: sleep disorders, insomnia

Nervous system disorders:

Uncommon: restlessness, excitability, irritability

Cardiac disorders:

Uncommon: reflex bradycardia;

Rare: tachycardia

Gastrointestinal disorders:

Common: heartburn, stomatitis

Hepatobiliary disorders:

Rare: Hepatic function abnormal, raised liver enzymes

Respiratory, thoracic and mediastinal disorders:

Unknown: Respiratory failure

Skin and subcutaneous tissue disorders:

Common: flushing, skin rash

Unknown: There have been cases of serious skin reactions, including Stevens Johnson Syndromeand Toxic Epidermal Necrolysis, associated with the use of midodrine.

Vascular disorders:

Common: supine hypertension (blood pressure above 180/110mmhg) with daily doses above30mg;

Uncommon: supine hypertension (blood pressure above 180/110mmhg) with daily doses above7.5mg.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There are literature reports of adults ingesting from 50 mg to 350 mg midodrine as a singledose. Severe hypertension and bradycardia may occur.

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

Treatment: In addition to the main general supportive care measures, induced vomiting and theadministration of an α-sympatholytic agent (e.g. nitroprusside, phentolamine, glyceryl trinitrate) 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.

For information on the management of overdose, contact the Poisons Information Centre on13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIESMechanism of action

Midodrine is the rapidly absorbed prodrug 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 isalso present, though this contributes almost nothing to the desired effect.

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

Nonclinical experiments showed that midodrine had a selective effect on blood flow in variousvascular beds, with the most effect observed in the femoral artery, and least in the mesenteric artery.

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 sphinctermuscle tone.

Desglymidodrine has no β-adrenergic effects.

Clinical trials

The safety and efficacy of midodrine was evaluated in a published randomised, double-blind,parallel group Phase III study (Low 1997, n=171) in patients with orthostatic hypotension of any aetiology. Patients were included based on a measured reduction of supine-to-standing systolic blood pressure (BP) of at least 15 mmHg and symptoms of dizziness, lightheadedness and/or unsteadiness (collectively referred to as lightheadness). Patients with pre-existing sustained supine hypertension above 180/110 mmHg were excluded. Concomitant treatment with fludrocortisone acetate, high-salt diet and compression garmentswas permitted during the study.

The study design included a single-blind placebo one week run in period, a double-blind three week treatment period (midodrine 10 mg or placebo three times a day), and a two weeksingle-blind placebo washout period. The primary efficacy endpoints were improvement in standing blood pressure (BP) and patients' recollection of symptoms of lightheadedness at weekly visits. The secondary endpoint was a global composite orthostatic symptom score independently rated by the investigator and the patient at the end of the treatment period which comprised of lightheadedness symptoms and improvements in the patients' ability to remain on their feet and perform orthostatic activities of daily living.

The mean age of patients was 60 years and the common underlying diagnoses were autonomic failure (Shy-Drager and Bradbury-Eggleston syndromes), diabetic autonomic neuropathy and Parkinson's disease. The study completion rate was 72% for the midodrinegroup (n=59/82) and 90% for the placebo group, which was due to a higher rate number ofadverse events in the midodrine group (refer to section 4.8 Adverse effects (Undesirable effects).

The supine and standing BP was measured before and one hour after the dose on week 2 to week 6 are shown in Table 3. The standing BP was significantly improved in the midodrine group compared with the placebo group ($p<0.001$) during the treatment period. The mean increase in systolic BP was 21.8 mmHg for midodrine-treated patients, which was maintainedthroughout the duration of the treatment period and returned toward baseline during the washout period. A similar pattern of improvement was observed for diastolic BP. The percentage change in standing BP was approximately double the change in supine BP.

Both groups showed an improvement in symptoms during treatment relative to baseline. The mean improvement for the midodrine group was statistically greater than the placebo group atthe end of the second week of treatment ($p=0.02$) and approached significance at the end of the third week ($p=0.06$). The improvement in the global composite orthostatic symptom scoreby investigators and patients also favoured midodrine treatment.

Table 3 - Mean (% change) supine and standing blood pressure (BP, mmHg) responses in the Phase III study* (Low 1997)

Visit	Midodrine				Placebo			
	No.	Change in BP supine	No.	Change in BP standing	No.	Change in BP supine	No.	Change in BP standing
Systolic BP								
Single-blind placebo	77	-0.1 (1)	75	-3.0 (3)	82	21 (1)	81	-2.0 (2)
Day 1 washout	55	12.0 (8)†	53	16.5 (17)†	73	1.8 (1)	71	3.2 (3)
Diastolic BP								
Single-blind placebo	77	0.6 (1)	68	-0.7 (1)	81	-2.0 (2)	76	2.1 (3)
Day 1 washout	55	5.5 (6)	48	7.9 (12)†	71	3.2 (0)	67	0.0 (0)

*Values represent mean data (mmHg with percent change in parentheses) from all evaluable subjects at eachtime point.
BP indicates blood pressure.
†$p<0.01$ versus placebo
‡Day 1 of washout period scored on the antecedent (pre-washout) period.

The clinical benefit of midodrine was evaluated in a published randomised, double-blind, placebo-controlled, post-marketing study (Smith 2016[4]) in patients with severe symptomatic OH. The objective of the study was to assess the effect of midodrine on symptom response inthe form of time to onset of syncopal symptoms or near-syncope measured using a protocol- defined tilt-table test at 1 h post-dose. Patients were eligible for the study if they were aged 18 years and older with a documented history of severe symptomatic OH (e.g. due to Parkinson's disease, Shy-Drager syndrome, multiple system atrophy, pure autonomic failure,or autonomic neuropathies). Patients must have been maintained on a stable dose of midodrine for at least 3 months, been ambulatory when receiving adequate therapy for their symptomatic OH and had at least one of the following symptoms while standing or when noton treatment: dizziness, lightheadedness, feeling faint, or feeling like they might lose consciousness. The sample size calculation for the study assumed a standard deviation of 240 s for within-patient difference in time to onset of syncopal symptoms or near syncope.

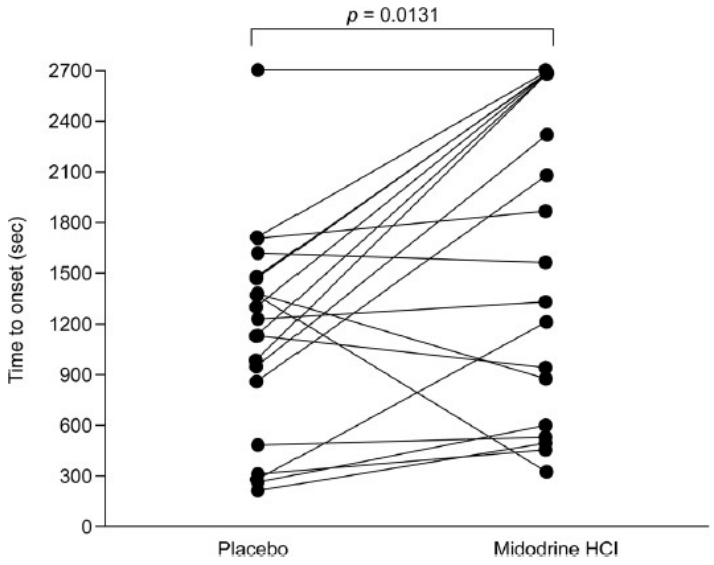
Using a power level of 80% and a two-sided significance level of 0.05, the sample size calculation determined that n=18 participants (n=9 per treatment sequence) would be neededto detect a treatment difference of 180 s between the treatments.

A total of 20 subjects were recruited, with 19 completing both arms. Patients were randomised into one of the two treatment sequences: midodrine followed by placebo or placebo followed by midodrine. Patients received midodrine at their pre-study dose or placebo and underwent a tilt-table test performed 1 h after administration of the treatment. The following day the alternative treatment was administered, and the tilt-table test was repeated 1 h after the treatment. The primary endpoint was the time to onset of syncopal symptoms or near-syncope (participants felt sufficiently dizzy, lightheaded, faint, or as if theywere about to lose consciousness so that they requested the table to be returned to horizontal, or they looked to be about to lose consciousness based on investigator assessment) during thetilt-table test.

The final analysis set included 19 patients who completed the cross-over treatments. One patient did not complete the study due to technical problems with the tilt-table. The mean ageof participants was 43.5 years (range 18-78) and the group was predominantly female (94.7%)). The pre-study midodrine dose was 2.5 mg to 15 mg. Treatment with midodrine resulted in a statistically significant increase in the time to tilt-table induced syncopal symptoms or near-syncopal symptoms relative to placebo control (p=0.0131). The least-squares mean time to onset of syncopal symptoms or near-syncope (mean ± SE) was 1626.6 ± 186.8 s after initiation of the tilt-table test after midodrine treatment and1105.6 ± 186.8 s after the placebo (Figure 1).

[4] Smith W, Wan H, Much D, et al. Clinical benefit of midodrine hydrochloride in symptomatic orthostatic hypotension: a phase 4, double-blind, placebo-controlled, randomized, tilt-table study. Clin Auton Res 2016;26:269–277.

Figure 1 - Time to onset of syncopal symptoms or near-syncope after initiation of the tilt-table test after placebo and midodrine treatment (Smith 2016)



5.2 PHARMACOKINETIC PROPERTIES

Absorption

The oral absorption of midodrine is facilitated by the intestinal coupled peptide transporter(PEPT1).

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 – 20 mg. Administration with food increases the AUC by approximately 25%, and the C_{max} decreasesby approximately 30%. The pharmacokinetics of desglymidodrine are not affected.

Distribution

Neither midodrine nor desglymidodrine 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 excretedin 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 mean plasma C_{max} of desglymidodrine, peaks in approximately 1 hour, with a plasma half-life of approximately 3 hours after the oral administration. 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 excretedin 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 approximately3 hours for desglymidodrine. Elimination of the active (-) enantiomer of desglymidodrine is slower than the elimination of the inactive (+) enantiomer.

5.3 PRECLINICAL SAFETY DATAGenotoxicity

Studies investigating the genotoxic potential of midodrine revealed no evidence of genotoxicity.

Carcinogenicity

In carcinogenic trials in rats an increased tumour incidence in the testicular interstitial cellswas observed; the relevance of this for humans is however unclear.

Long term studies have been conducted in rats and mice at dosages of 3 to 4 times the maximum recommended daily human dose on a mg/m^2 basis, with no indication of carcinogenic effects related to midodrine.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline

cellulose

Pregelatinised Maize Starch

Magnesium Stearate Colloidal anhydrous silica

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

27 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC-PVDC/Aluminium foil blister.

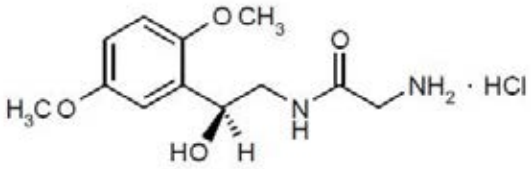
2.5 mg: Packs of tablets 60, 90 and 500 tablets.5 mg: Packs of tablets 60, 90 and 500 tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to yourlocal pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



and enantiomer

CAS number

43218-56-09

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Southern Cross Pharma Pty Ltd
Suite 5/118 church Street
Hawthorn VIC 3122

email: info@southernxp.com

9 DATE OF FIRST APPROVAL

4 December 2019

10 DATE OF REVISION

Not applicable