Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Midodrine Hydrochloride Aspire 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of midodrine hydrochloride.

Excipient with known effect:
Each tablet contains 0.8 mg Sunset Yellow Lake (E110).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Orange, round tablet, diameter approximately 7 mm with M5 debossed on one side and score line on the other side.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in adults for 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 3 times daily. 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. 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 3 divided doses. The maximum daily dose is 30 mg given in 3 divided doses. Doses in excess of 30 mg 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.

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 mm Hg 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 4.3).

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

Method of administration
For oral use.

4.3 Contraindications

Midodrine Hydrochloride Aspire 5 mg Tablets is contraindicated in patients with:

- Hypersensitivity to the active substance(s) 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 <30mL/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. The patients should be cautioned to report symptoms of supine hypertension immediately such as cardiac awareness, (palpitations, chest pain and 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 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).

Great caution should be exercised in patients with mild to moderate renal insufficiency (creatinine clearance >30mL/min and <90mL/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, increasing 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.

Midodrine Hydrochloride Aspire 5 mg Tablets contain Sunset Yellow colouring (E110) which can cause allergic-type reactions, including asthma. This allergy is more common in people who are allergic to aspirin.

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.

Sympathomimetics and other vasopressor agents
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 Hydrochloride Aspire 5 mg 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 (eg 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 are insufficient with respect to reproductive toxicity (see section 5.3). Midodrine Hydrochloride Aspire 5 mg Tablets 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 not known whether this drug is excreted in breast milk; this drug should not be given to nursing mothers.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or light headedness while receiving Midodrine Hydrochloride Aspire 5 mg Tablets should refrain from operating machinery.

4.8 Undesirable effects

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000), very rare (<1/10,000); Not known (cannot be estimated from the available data).

Psychiatric disorders
Uncommon: Sleep disorders, insomnia.
Not known: Anxiety, confusional state

Nervous system disorders
Common: Paraesthesia
Uncommon: Headache, restlessness, excitability, irritability.
Rare: Dizziness or light headedness.

Eye disorders

Rare: Visual disturbance.
Not known: Increased tear production.

Cardiac disorders
Uncommon: Reflex bradycardia.
Rare: Tachycardia, palpitations, arrhythmias, chest pain.

Vascular disorders
Common: Supine hypertension (Blood pressure above or equal to 180/110 mmHg) with daily doses above 30mg.
Uncommon: Supine hypertension (Blood pressure above or equal to 180/110 mmHg) with daily doses up to 7.5mg.
Rare: Cerebrovascular accident.

Gastrointestinal disorders
Common: Nausea, dyspepsia, vomiting, stomatitis.
Uncommon: Abdominal pain.
Not known: Diarrhoea

Hepatobiliary disorders
Rare: Hepatic function abnormal, raised liver enzymes.
Skin and subcutaneous tissue disorders
Very common: Piloerection.
Common: Chills, skin rash, pruritus (mainly of the scalp), flushing.

Renal and Urinary disorders
Very common: Dysuria.
Common: Urinary retention.
Uncommon: 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie ; E-mail: medsafety@hpra.ie.

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 dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents
ATC-code: C01C A17

A directly - acting alpha sympathomimetic agent which enhances vascular smooth muscle tone leading to a pressor response after oral administration. The major biological activity resides in the main metabolite desglymidodrine.

A 6 week study with a 3 week double blind period of midodrine 10 mg t.i.d. (three times a day) versus placebo, in patients with orthostatic hypotension due to autonomic dysfunction indicated that midodrine significantly, increased standing systolic blood pressure and improved dizziness/unsteadiness compared to placebo.

Two open long-term studies have been conducted with midodrine. 693 subjects with orthostatic hypotension from the Bradbury-Eggleston Syndrome (28%), from renal failure, syncope, autonomic neuropathy and AIDS (33%) and from other causes (39%), received an average total daily dose of midodrine 17-24 mg over periods up to one year. 52% completed one year of study.

The primary efficacy variables were the quality-of-life questionnaire evaluating the symptoms as indicated in the enclosed table, the improvement in standing blood pressure and the investigators global opinion. In the quality-of-life index (QOLI) all questions were answered using a three point scale; 1 = symptom occurred often, 2 = symptom occurred sometimes, 3 = symptom never occurred. At each visit the subject's blood pressure was measured before taking a dose of midodrine and one hour thereafter. The investigators global opinion was recorded at the end of the study. The investigator assessed the subject's ability to perform daily activities. Summary statistics only were provided.

The percentage change in the QOLI is indicated in the table. Improvement was seen in the standing blood pressure. The systolic blood pressure was increased by 12mm of mercury, while the diastolic blood pressure was improved by 6-7 mm of mercury. The investigator stated that at the end of the study 52% of subjects had good to excellent ability to perform daily activities.

It is important to note that subjects did continue to take previous medications including steroids.

102 subjects died during this long-term open-ended trial however none of the deaths was reported to be drug related. It is important to note that most of these patients had considerable impairment of cardiac function. The most common adverse events apart from deaths were headache in 5%, supine hypertension in 6%, piloerection in 5% and pruritus of the scalp in 10%. There were no clinically significant effects of midodrine on laboratory test results or on the electrocardiogram.

Table 1

Symptom	N	Baseline Mean (SEM)	End of Study Mean (SEM)	Change Mean (SEM)	% Change
Dizziness or light headedness	524	1.4 (0.02)	1.9 (0.03)	0.42 (0.034)	30 %
Weakness or fatigue	524	1.3 (0.02)	1.6 (0.03)	0.30 (0.030)	23 %
Blurred vision	520	1.9 (0.03)	2.3 (0.03)	0.32 (0.035)	17 %
Faint	521	2.1 (0.03)	2.5 (0.03)	0.36 (0.034)	17 %
Energy level	519	1.3 (0.03)	2.2 (0.03)	0.86 (0.043)	66 %
Ability to stand for greater than 15 min.	520	1.6 (0.03)	1.9 (0.03)	0.24 (0.033)	15 %
Ability to walk unassisted	518	1.9 (0.04)	2.0 (0.04)	0.11 (0.033)	6 %
Depression	519	2.1 (0.03)	2.2 (0.03)	0.08 (0.031)	4 %
QOLI	524	1.7 (0.02)	2.1 (0.02)	0.33 (0.021)	19 %

In a second long-term study 723 patients with neurogenic orthostatic hypotension received an average total daily dose of 18 mg of midodrine over a one-year period. Up to 196 patients took the medication for a period equal to or greater than one year. The primary efficacy event was the change in standing blood pressure. The baseline systolic and diastolic pressures were the last measurements taken prior to the first dose of midodrine. End point systolic and diastolic pressures were the final measurements taken during treatment with midodrine. Summary statistics were provided.

At the end point the mean standing systolic blood pressure had increased by 8 mm of mercury from baseline with an increase in the diastolic blood pressure by nearly 5 mm of mercury.

It is important to note that subjects did continue to take previous medications including steroids.

There was a 6% death rate. In all cases the relationship to midodrine was judged as none or unlikely. The most common adverse events other than death reported in this study were syncope and scalp pruritus.

5.2 Pharmacokinetic properties

Excretion occurs primarily via the kidney in the form of metabolites. Plasma t½ of the parent drug is 1 hour and of the main metabolite 3½ hours.

5.3 Preclinical safety data

No relevant information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline (E460)
Maize starch (E1404)
Magnesium stearate (E470b)
Silica colloidal anhydrous (E551)
Sunset yellow lake (E110)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Clear PVC-PVDC-aluminium foil blisters containing 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100, 112 or 120 tablets.
Not all packs 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

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8 MARKETING AUTHORISATION NUMBER

PA23142/008/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th September 2022

10 DATE OF REVISION OF THE TEXT

May 2025