



**Australian Government**  
**Department of Health**  
Therapeutic Goods Administration

# Australian Public Assessment Report for Midodrine hydrochloride

Proprietary Product Name: Vasodrine /  
Midodrine SCP / Midodrine ANS

Sponsor: Southern Cross Pharma Pty Ltd

**July 2021**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

## About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

<b>List of abbreviations</b>	<b>4</b>
<b>I. Introduction to product submission</b>	<b>6</b>
Submission details _____	6
Product background _____	7
Regulatory status _____	8
Product Information _____	9
<b>II. Registration timeline</b>	<b>9</b>
<b>III. Submission overview and risk/benefit assessment</b>	<b>10</b>
Quality _____	10
Nonclinical _____	11
Clinical _____	12
Risk management plan _____	21
Risk-benefit analysis _____	22
Outcome _____	26
<b>Attachments 1, 2 and 3. Product Information</b>	<b>27</b>

## List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the plasma concentration-time curve
AUS	Australian
BD	Twice daily
BP	Blood pressure
CI	Confidence interval
C <sub>max</sub>	Maximum plasma concentration
CPMP	Committee for Proprietary Medicinal Products, European Medicines Agency (European Union)
CYP	Cytochrome P450
DBP	Diastolic blood pressure
EMA	European Medicines Agency (European Union)
EU	European Union
FAERS	Food and Drug Administration Adverse Event Reporting System (United States of America)
FDA	Food and Drug Administration (United States of America)
LBS	Literature-based submission
MAP	Mean arterial pressure
NOH	Neurogenic orthostatic hypertension
OH	Orthostatic hypertension
PAF	Pure autonomic failure
PD	Pharmacodynamic(s)
PEPT1	Peptide transporter 1

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Abbreviation	Meaning
PSUR	Periodic safety update report
SAS	Special Access Scheme
SBP	Systolic blood pressure
TDS	Three times a day
UK	United Kingdom
US(A)	United States (of America)

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New chemical entity
<i>Product names:</i>	Midodrine SCP, Midodrine ANS, Vasodrine
<i>Active ingredient:</i>	Midodrine hydrochloride
<i>Decision:</i>	Approved
<i>Date of decision:</i>	4 December 2019
<i>Date of entry onto ARTG:</i>	18 December 2019
<i>ARTG numbers:</i>	309179, 309180, 309181, 309182, 309183, 309184
<i>, Black Triangle Scheme:<sup>1</sup></i>	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
<i>Sponsor's name and address:</i>	Southern Cross Pharma Pty Ltd <sup>2</sup> Suite 5/118 Church Street Hawthorn VIC 3122
<i>Dose form:</i>	Tablet
<i>Strengths:</i>	2.5 mg and 5 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	60, 90 and 500 tablets
<i>Approved therapeutic use:</i>	<i>Midodrine SCP / Midodrine ANS / Vasodrine is indicated in adults for the treatment of severe symptomatic orthostatic hypotension due to autonomic dysfunction when exacerbating factors have been addressed and other forms of treatment remain inadequate.</i>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	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 orthostatic hypotension.

<sup>1</sup> The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

<sup>2</sup> Following approval, sponsorship of the products was transferred to Southern XP IP Pty Ltd, Unit 5/118 Church Street, Hawthorn, VIC 3122.

*Initial dose:* 2.5 mg three 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.

The maximum recommended dose should not exceed 30 mg daily.

For further information refer to the Product Information.

*Pregnancy category:*

C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

## Product background

This AusPAR describes the application by Southern Cross Pharma Pty Ltd (the sponsor)<sup>2</sup> to register Midodrine SCP/Midodrine ANS/Vasodrine (midodrine hydrochloride) 2.5 mg and 5 mg tablets for the following proposed indication:

*For the treatment of orthostatic hypotension in adults.*

Orthostatic hypertension (OH) is a manifestation of autonomic dysfunction associated with failure of cardiovascular adaptive mechanisms that compensate for the reduction in venous return to the heart when a person resumes an upright position. In healthy subjects, cardiac output and blood pressure (BP) are maintained on standing via activation of autonomic neural and hormonal reflex mechanisms that compensate for the impaired venous return. Failure of these mechanisms can result in OH.

OH may be subdivided into two main categories; structural and functional. Structural (or neurogenic) OH is due to a chronic autonomic failure related to pure autonomic failure (PAF), multiple system atrophy, Parkinson's disease, or secondary to diabetes, renal dysfunction and amyloidosis. Functional impairment of the autonomic system can be associated with heart failure, medicines such as tricyclic antidepressants or diuretics, and absolute or relative reduction in circulating blood volume.

Classic OH is defined as a sustained reduction of at least 20 mmHg in systolic blood pressure (SBP) or decrease in diastolic blood pressure (DBP) of at least 10 mmHg, within 30 to 180 seconds of active standing or during a tilt table test of  $\geq 60$  degrees.<sup>3</sup> The condition is diagnosed by demonstrating a significant and persistent fall in BP either by the bedside active standing test, or the head-up tilting test.

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<sup>3</sup> The **tilt table test**, also known as a head-up tilt test, is used to study vasovagal reactions in patients with unexplained syncope. A patient's blood pressure, heart rate and heart rhythm are recorded as a table adjusts their position from horizontal to vertical.

The sponsor proposes to register the new chemical entity midodrine hydrochloride in 2.5 mg and 5 mg tablet forms for the treatment of OH.

Midodrine hydrochloride is a first in class selective  $\alpha$ 1-receptor agonist, a sympathomimetic agent that selectively stimulates the alpha-1 adrenergic receptor. Midodrine is a prodrug of the pharmacologically active constituent desglymidodrine. Desglymidodrine increases peripheral arterial resistance resulting in an increase in arterial blood pressure.

This submission is a literature-based submission (LBS), as agreed with the TGA.

## Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

Midodrine hydrochloride has been available internationally for over 20 years as a treatment for OH. Midodrine hydrochloride was first registered by the Food and Drug Administration (FDA) in the United States of America (USA) in 1996 under its Accelerated-Approval Process mechanism which allows products with a surrogate endpoint(s) to be registered for serious conditions that fulfil an unmet medical need. Shire Development, the United States (US) innovator, discontinued manufacturing its product (tradename: ProAmatine) in 2003 when its orphan exclusivity period expired. Generic versions of midodrine hydrochloride were registered in the USA between 2003 and 2006, and these registrations remain active. Midodrine hydrochloride was registered for treatment of OH in the European Union (EU; including the United Kingdom (UK) at that time, and the Netherlands, under a decentralised procedure), and New Zealand. In Canada, there are two registered generics but the innovator cancelled their registration for reasons unknown. The approved indications for midodrine hydrochloride in the EU, USA, Canada and New Zealand are described below.

**Table 1: International regulatory status of midodrine hydrochloride tablets for the treatment of orthostatic hypotension**

Jurisdiction	Approved indications
EU	<i>Midodrine hydrochloride 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.</i>
USA	<i>ProAmatine is indicated for the treatment of symptomatic orthostatic hypotension (OH). Because ProAmatine can cause marked elevation of supine blood pressure (BP &gt; 200 mmHg systolic), it should be used in patients whose lives are considerably impaired despite standard clinical care, including non-pharmacologic treatment (such as support stockings), fluid expansion, and lifestyle alterations. The indication is based on ProAmatine's effect on increases in 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit.</i>



Jurisdiction	Approved indications
Canada	<i>Midodrine (midodrine hydrochloride) may be used to attenuate symptoms of chronic orthostatic hypotension due to autonomic failure in patients with Bradbury-Eggleston syndrome, Shy-Drager syndrome, diabetes mellitus disease and Parkinson's disease. The initiation and up-titration of midodrine therapy should be undertaken under close medical supervision in a controlled clinical setting.</i>
New Zealand	<i>Gutron (midodrine hydrochloride) is indicated to attenuate symptoms of chronic orthostatic hypotension due to autonomic failure in patients with Bradbury-Eggleston or Shy-Drager syndromes and other medical disorders such as diabetes mellitus or Parkinson's disease. Because midodrine 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 lifestyle alterations.</i>

## Product Information

The Product Information (PI) documents approved with the submission which is described in this AusPAR can be found as Attachments 1, 2 and 3 for the three respective approved tradenames for this submission. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

**Table 2: Timeline for Submission PM-2018-02754-1-3**

Description	Date
Submission dossier accepted and first round evaluation commenced	2 October 2018
First round evaluation completed	29 April 2019
Sponsor provides responses on questions raised in first round evaluation	9 July 2019
Second round evaluation completed	14 August 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	9 September 2019
Sponsor's pre-Advisory Committee response	15 September 2019
Advisory Committee meeting	4 October 2019

Description	Date
Registration decision (Outcome)	4 December 2019
Completion of administrative activities and registration on the ARTG	18 December 2019
Number of working days from submission dossier acceptance to registration decision*	247

\*Statutory timeframe for standard applications is 255 working days

### III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

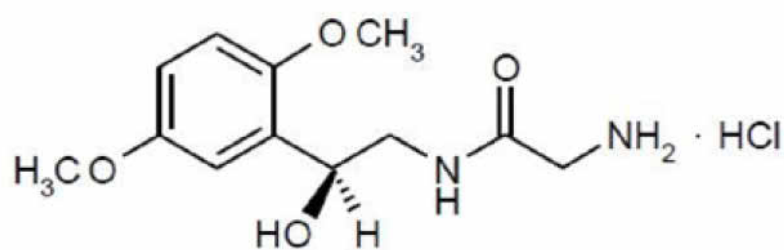
The Delegate referred to the following guidance documents:

- TGA, Guidance on literature-based submissions, 27 May 2014. Available from the TGA website.
- European Medicines Agency (EMA), Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study, 31 May 2001.<sup>4</sup>
- EU, Clinical Investigation of Medicinal Products for Long-Term Use. (last revised February 1987).<sup>5</sup>

#### Quality

The structure of midodrine hydrochloride is shown below in Figure 1.

**Figure 1: Chemical structure of midodrine hydrochloride**



and enantiomer

The chemical formula of midodrine hydrochloride is  $C_{12}H_{18}N_2O_4 \cdot HCl$ . It has a molecular weight of 290.74 and a Chemical Abstracts Service (CAS) registry number of 3092-17-9. The active pharmaceutical ingredient contains one chiral centre and the drug substance is available as the racemic mixture.

<sup>4</sup> EMA, Committee for Proprietary Medicinal Products (CPMP), Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study CPMP/EWP/2330/99, 31 May 2001.

<sup>5</sup> Clinical Investigation of Medicinal Products for Long-Term Use: Directive 75/318/EEC as amended (last revised February 1987). Available from the TGA website.

The proposed products are white, round tablets debossed with the strength on one side. They are to be packaged in blisters in packs of 60 and 90. The excipients are microcrystalline cellulose, pregelatinised maize starch, magnesium stearate and colloidal anhydrous silica.

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

Following the resolution of all outstanding issues, the quality evaluator has recommended approval from a pharmaceutical chemistry and quality control aspect.

No additional conditions of registration have been requested by the quality evaluator.

## Nonclinical

The nonclinical information was composed entirely of published literature. The nonclinical evaluator states that there was a lack of primary data for the pharmacokinetics (PK) of midodrine hydrochloride in nonclinical models, the toxicological effects of repeated dosing of midodrine hydrochloride and the effects of midodrine hydrochloride on genotoxicity, carcinogenicity and reproductive toxicity. The primary data provided was insufficient to support the registration of midodrine hydrochloride as all of the toxicology, genotoxicity; carcinogenicity and reproductive toxicity information were purely based on the foreign PI documents for midodrine hydrochloride. However, the nonclinical evaluator has indicated that the information provided raised no novel safety concerns for the use of midodrine hydrochloride for the intended indication and may potentially be compensated for by the long history of clinical use overseas.

Safety pharmacology studies identified a small, but significant increase in the QT interval.<sup>6</sup> Peptide transporter 1 (PEPT1)-mediated absorption of midodrine hydrochloride indicates the potential for substrate competition and altered absorption kinetics of xenobiotics via the PEPT1 transporter. Inducers or inhibitors of cytochrome P450 (CYP);<sup>7</sup> 2D6 may alter desglymidodrine exposure and desglymidodrine may affect the exposure kinetics of xenobiotics that are metabolised by CYP2D6.

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<sup>6</sup> The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

**The corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

<sup>7</sup> **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

## Clinical

The clinical data consisted of the following literature references:

- Contributing pharmacology data:
  - four PK studies
  - four pharmacodynamics (PD) studies.
- Contributing efficacy data:
  - nine randomised controlled trials
  - two meta-analyses
  - three other efficacy studies
  - one uncontrolled long-term study
  - four systematic reviews.
- Contributing safety data
  - six randomised controlled trials
  - two meta-analyses
  - one uncontrolled long-term neuronal OH study
  - two pharmacology
  - one other efficacy study
  - two other studies
  - five studies with evaluable safety data only.

## Pharmacology

### *Pharmacokinetics*

Midodrine is rapidly absorbed after oral administration, with an absolute bioavailability of 93% (measured as desglymidodrine). Bioavailability of desglymidodrine is not affected by food. In healthy adults, there are dose-proportional increases in maximum plasma concentration ( $C_{max}$ ) and area under the plasma concentration-time curve (AUC) for single oral midodrine doses across the 2.5 to 20 mg dose range. International PI documents recommend midodrine is taken at least 4 hours before bed-time to prevent supine hypertension.

The volume of distribution following an oral dose of 2.5 mg midodrine tablets was  $353 \pm 80$  L. Midodrine and desglymidodrine are not significantly bound to plasma proteins. Peak plasma concentrations are reached between 15 to 30 minutes for midodrine and between 1 to 2 hours for desglymidodrine.

Midodrine is partially hydrolysed before absorption from the gastrointestinal tract and metabolised by the liver into desglymidodrine. Deglycation of midodrine to desglymidodrine takes place in many tissues, and both compounds are metabolised in part by the liver. *In vitro* studies have shown that the human liver microsomes, CYP2D6, CYP1A2 and CYP2C19, exhibited large catalytic activity of desglymidodrine to the 5'-O-demethylation of desglymidodrine. Elimination of desglymidodrine is primarily caused by oxidative metabolism, followed by (partial) conjugation.

Midodrine, desglymidodrine and their degradation products are excreted in the urine by more than 90% within 24 hours in conjugated or non-conjugated forms. Plasma

elimination half-life for midodrine and desglymidodrine is approximately 30 minutes and 2 to 4 hours, respectively.

In the target population, absorption was similar to that seen in healthy adult volunteers. There was a dose-proportional increase in  $C_{max}$  over the midodrine oral dose range of 2.5 to 20 mg. Compared with healthy volunteers, some subjects with neurogenic OH (NOH) had a more prolonged time to maximum plasma concentration ( $T_{max}$ ). The  $C_{max}$  for desglymidodrine was dose-proportional over the oral dose range of 2.5 to 20 mg. The estimated 30 minute half-life of midodrine was consistent with healthy volunteers, the half-life of desglymidodrine was more prolonged at approximately 4 hours.

No multiple dose PK studies have been published.

### **Pharmacodynamics**

The (-) enantiomer of desglymidodrine is active and the (+) enantiomer is inactive. Desglymidodrine diffuses poorly across the blood-brain barrier, and is not associated with effects on the central nervous system. Desglymidodrine does not stimulate cardiac beta-adrenergic receptors.

The primary PD study results for standing SBP were mixed, although the results were based on small subject numbers. Grobecker and Kees (1993)<sup>8</sup> and Wright et al. (1998)<sup>9</sup> provided the strongest evidence of a dose-response relationship for increased standing SBP across the midodrine dose range 2.5 mg to 20 mg, with optimal efficacy most likely with a 10 mg three times a day (TDS) regimen. The treatment effects on standing SBP lasted between 1 to 4 hours at therapeutic doses. A drop in heart rate (reflex bradycardia) was consistently observed across most primary PD studies.

Wright et al. (1998)<sup>9</sup> observed a dose-proportional increase in the incidence of supine hypertension (supine SBP > 200 mmHg), across the midodrine dose range 2.5 mg to 20 mg. No other cases of supine hypertension were observed in either the PK studies or the other PD studies included in the clinical dossier.

Two secondary PD studies provided consistent observations that noradrenaline concentrations decreased and atrial natriuretic peptide concentrations increased during orthostasis. Furthermore, these effects appeared to be independent of BP. The clinical significance of these effects on efficacy and safety of midodrine treatment remain unclear.

No specific QT/QTc study;<sup>6</sup> was undertaken so the effect of midodrine on QT liability/QT prolongation could not be fully assessed.

### **Dose ranging**

The sponsor was not the innovator for midodrine and did not have access to the clinical study reports from the clinical development program. Wright et al (1998)<sup>9</sup> demonstrated that the 2.5 mg midodrine dose regimen did not provide statistically or clinically meaningful results, but significant effects of midodrine versus placebo were found at 1 hour post-dose for 10 mg and 20 mg midodrine, which persisted until 4 hours post-dose for the 20 mg strength. The frequency and severity of adverse events (AEs) were dose related with the most severe reactions occurring with the 20 mg dose. The maximum tolerated dose appeared to be 10 mg. A 5 mg or 7.5 mg dose regimen was not fully assessed hence the minimum effective dose remains unclear.

Midodrine dosing is usually recommended during daytime hours. Administration of midodrine after 6 pm, and the evening meal, is not recommended since a higher incidence

<sup>8</sup> Grobecker, H.F. and Kees, F. Pharmacokinetic parameters and haemodynamic actions of midodrine in young volunteers. *International Angiology*, 1993; 12: 119-124.

<sup>9</sup> Wright, R.A. et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology*, 1998; 51: 120-124.

of supine hypertension has been observed. The evaluator considered the TDS dose regimen is appropriate given the 4 hour half-life.

## **Efficacy**

The sponsor listed Wright et al. (1998)<sup>9</sup> and Smith et al (2016)<sup>10</sup> as pivotal studies in the draft PI. The evaluator was not satisfied that these studies met the definition of pivotal as per the relevant TGA adopted EU guideline.<sup>4</sup> The individual articles listed in the Parsaik et al. (2013)<sup>11</sup> and Izcovich et al (2014)<sup>12</sup> meta-analyses were requested by the evaluator and Low et al (1997)<sup>13</sup> was identified as the main Phase III efficacy study. Five other studies that provided efficacy data were also identified. In summary, the evaluator considered there to be one main efficacy study, nine other efficacy studies, four studies for other indications and two meta-analyses.

### **Main efficacy study**

#### *Low et al. (1997)*

Low et al (1997);<sup>13</sup> was a randomised, double blind, parallel group trial that evaluated the efficacy of a 10 mg TDS dose of midodrine in improving BP and symptoms in patients with NOH. The study consisted of a 1 week single blind placebo run-in period, a 3 week double blind period, and a 2 week single blind placebo washout. Adults with symptomatic NOH, with an orthostatic reduction of at least 15 mmHg were eligible for study inclusion. Concomitant treatment with fludrocortisone acetate, high-salt diet, and compression garments was allowed. 50.6% of placebo subjects and 40.2% of midodrine subjects took fludrocortisone. 19.1% of placebo subjects and 22.0% of midodrine subjects wore compression garments.

The analysis populations were not defined, but 192 patients were registered, 186 received placebo intervention, 171 patients were randomised (89 to placebo, 82 to midodrine) and 162 patients were considered evaluable. 72.0% and 90.0% of subjects completed treatment in the midodrine and placebo groups, respectively. Baseline demographics and disease characteristics of the evaluable population were similar, although the midodrine group had 14% more people with diabetes mellitus and the placebo group had more cases of Bradbury-Eggleston syndrome and Shy-Drager syndrome.

The primary efficacy variables were improvement in standing SBP, and symptoms of light-headedness. The primary efficacy endpoints were assessed at the end of double blind treatment. Standing SBP in the midodrine treatment group was statistically significantly greater than in the placebo treatment group at every time point in the double blind treatment phase (all  $p < 0.001$ ), with a mean of 21.8 mmHg (to SBP of 118 mmHg). The treatment effect was maintained throughout the double blind period and returned toward baseline upon completion of placebo washout. Changes in supine SBP and standing and supine DBP were consistent with standing SBP changes. The mean symptom score for light-headedness generally improved throughout the double blind treatment phase in both groups compared to Baseline. Midodrine treatment was statistically significantly superior to placebo treatment at the end of Week 2 of the double blind treatment phase ( $p = 0.02$ ), with borderline statistical significance achieved at the end of double blind treatment ( $p = 0.06$ ).

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<sup>10</sup> Smith W 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.

<sup>11</sup> Parsaik AK et al. Midodrine for orthostatic hypotension: a systematic review and meta-analysis of clinical trials. *J Gen Intern Med*, 2013; 28 (11): 1496-1503.

<sup>12</sup> Izcovich A et al. Midodrine for orthostatic hypotension and recurrent reflex syncope: a systematic review. *Neurology*, 2014; 83: 1170-1177.

<sup>13</sup> Low et al. Efficacy of midodrine versus placebo in neurogenic orthostatic hypotension: A randomized, double-blind multicentre study. *JAMA*, 1997; 277: 1046-1051.

The secondary efficacy endpoints were global symptom relief score by investigator and patient. The global evaluation was significantly better for midodrine-treated patients, evaluated at the end of the double blind treatment period according to both investigator ( $p < 0.001$ ) and patient ( $p = 0.03$ ). The mean score for midodrine was 2.8 by investigator and 2.7 by patient, being significantly greater than the mean values for placebo by investigator (2.0) or patient (2.2).

### ***Other efficacy studies***

#### *Wright et al. (1998)*

Wright et al (1998)<sup>9</sup> was a Phase I/II dose ranging study for patients with NOH. The study was a randomised, double blind, placebo-controlled, four-way crossover, single dose trial. Eligible subjects had a supine to standing BP drop of  $\geq 15$  mmHg and symptoms of OH or other pre-syncope symptoms. Patients were randomised to one of four sequences describing the order in which the matching placebo and midodrine doses were taken (2.5 mg, 10 mg and 20 mg). Patients were given one oral dose of study medication each day. Nine patients took fludrocortisone throughout the study. The primary efficacy endpoint was the change in standing SBP induced by midodrine at 1 hour, compared with placebo. Standing blood pressures were measured one minute after arising, after the patient had been supine for at least 20 minutes, at Baseline and 1, 2, 3, 4, 5 and 6 hours post-treatment. Supine pressures were measured pre-dose and every 0.5 hours post-dose for 6 hours. The study included 25 subjects, mean age 62 years (range: 38 to 78 years), mostly female (56%) and with pure autonomic failure the most common diagnostic group.

Mean increases in standing SBP 1 hour post-dose were: 5 mmHg (placebo); 7 mmHg (2.5 mg midodrine); 34 mmHg (10 mg midodrine) and 43 mmHg (20 mg midodrine). The mean increases in standing SBP demonstrated a linear relationship to the log dose of midodrine. The duration of action of midodrine demonstrated that both 10 mg and 20 mg doses significantly increased standing SBP at 1 hour and the effect was maintained up to 4 hours for the 20 mg dose.

#### *Smith et al. (2016)*

Smith et al. (2016);<sup>10</sup> was a randomised, double blind, placebo-controlled, multicentre, Phase IV cross-over trial in patients with severe symptomatic OH to assess the effect of midodrine on time to onset of syncopal symptoms or near-syncope measured using a tilt-table test 1 hour post-dose. Subjects were maintained on a stable dose of midodrine for at least 3 months and had  $\geq 1$  OH symptom while standing or off treatment. There was an initial open label screening phase in which patients continued their pre-study midodrine dose. Midodrine was withdrawn (known as Part A) and eligible patients were randomised (known as Part B) to receive: midodrine followed by placebo or placebo followed by midodrine. The pre-study midodrine dose was then reinstated. The study included 20 patients (mean age 43.5 years (range: 18 to 78), female (94.7%), white (84.2%), pre-trial midodrine dose range 2.5 to 15 mg, multiple diagnoses) and the final analysis set included 19 subjects.

The primary efficacy endpoint was time to onset of syncopal symptoms or near-syncope during the tilt-table test. On average, 26% more subjects on midodrine treatment completed the tilt test than patients who received placebo treatment. The least-squares mean time to onset of syncopal symptoms or near-syncope (mean  $\pm$  standard error) was  $1626.6 \pm 186.8$  seconds after initiation of the tilt-table test after midodrine treatment and  $1105.6 \pm 186.8$  seconds after placebo. 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 ( $p = 0.0131$ ).

*Jankovic et al. (1993)*

Jankovic et al. (1993);<sup>14</sup> was a randomised, double blind, placebo-controlled, multicentre, parallel-group study in moderate to severe OH due to progressive autonomic failure. Patients had to demonstrate a decrease in BP  $\geq 15$  mmHg (supine to standing position) prior to double blind treatment and/or at least two symptoms of OH, and a history of syncope or near syncope. After a 1 week single blind placebo run-in phase patients were randomised to receive 4 weeks double blind placebo, midodrine 2.5 mg, 5 mg or 10 mg TDS. The midodrine 5 mg or 10 mg groups received dose titration at weekly intervals by 2.5 mg increments until the designated dose was reached. Concomitant fludrocortisone and other non-drug treatments were permitted. The primary efficacy endpoints were improvement at 1 hour post-dose in standing SBP and improvement of symptoms of OH. Standing BP and heart rate were taken 1 minute after the patient had assumed an upright posture. A total of 97 subjects were enrolled with mean age 61 years (range: 22 to 86 years) and most subjects were male (54.6%). The final analysis population comprised of 75 patients.

Midodrine (10 mg) significantly increased standing SBP by 22 mmHg (28%) versus placebo ( $p < 0.001$ ; number needed to treat (NNT) 4).<sup>15</sup> Midodrine improved the following symptoms of OH compared to placebo based on 63 of 97 questionnaires:

- 2.5 mg: standing time ( $p < 0.05$ )
- 5 mg: dizziness/light-headedness, weakness/fatigue and impaired ability to stand ( $p < 0.05$ )
- 10 mg: syncope and feelings of depression (both  $p < 0.05$ ) and energy level ( $p < 0.001$ ).

Midodrine 10 mg significantly increased standing DBP by 15 mmHg versus placebo ( $p < 0.001$ ); supine SBP by 13 mmHg versus placebo ( $p < 0.001$ ) and supine DBP by 5 mmHg ( $p < 0.001$ ). There was no appreciable effect on supine or standing heart rates across treatments.

*Byun et al. (2017)*

Byun et al. (2017);<sup>16</sup> was a randomised, parallel group, open label study to evaluate the long-term (for up to 3 months) efficacy and safety of single-dose midodrine or pyridostigmine or combined treatment in adult patients with symptomatic NOH. Subjects had to demonstrate SBP of  $\geq 20$  mmHg or DBP  $\geq 10$  mmHg within 3 minutes of standing. Subjects were randomised 1:1:1 to receive single-dose midodrine (2.5 mg twice daily (BD)), pyridostigmine (30 mg BD) or combined treatment. The primary efficacy study endpoint was improvement of orthostatic BP drop after three months' treatment. Orthostatic BP and heart rate were measured after 10 minutes of rest in the supine position and at 1, 3, 5 and 10 minutes after standing at Baseline. Maximum decrements in SBP and DBP within 3 minutes of standing were recorded. The study enrolled 87 subjects (mean age 57.2 years, 47.1% male, idiopathic OH 47.1%). 66 (75%) patients completed the trial and 22 patients were lost to follow-up after 3 months.

<sup>14</sup> Jankovic et al. Neurogenic orthostatic hypotension: A double-blind placebo-controlled study with midodrine: *The American Journal of Medicine*, 1993; 95: 38-48.

<sup>15</sup> The **number needed to treat (NNT)** is the number of patients you need to treat in order for one person to achieve a positive outcome.

<sup>16</sup> Byun, J-I. et al. Efficacy of single or combined midodrine and pyridostigmine in orthostatic hypotension. *Neurology*, 2017; 89: 1078-1086.



At Baseline, the midodrine-only group had statistically significantly higher supine SBP ( $p = 0.004$ ) and DBP ( $p = 0.041$ ) than other treatment groups. After 3 months of treatment, the orthostatic SBP and DBP drops were significantly decreased relative to Baseline for all treatment groups:

- Midodrine only: SBP 50.6% reduction from -24.7 at Baseline to -12.2 mmHg at 3 months ( $p < 0.05$ ) and DBP 62.7% reduction from -13.4 at Baseline to -5.0 at 3 months ( $p < 0.05$ ).
- Pyridostigmine only: SBP 49.8% reduction from -23.3 at Baseline to -11.7 mmHg at 3 months ( $p < 0.05$ ) and DBP 72.9% reduction from -15.5 at Baseline to -4.2 at 3 months ( $p < 0.05$ ).
- Midodrine + pyridostigmine: SBP 47.1% reduction from -22.5 at Baseline to -11.9 mmHg at 3 months ( $p < 0.05$ ) and DBP 50.7% reduction from -13.4 at Baseline to -6.6 at 3 months ( $p < 0.05$ ).

*Ramirez et al. (2014)*

Ramirez et al. (2014);<sup>17</sup> was a randomised single blind, single centre cross-over study to compare the effect of acute atomoxetine versus midodrine on upright SBP and orthostatic symptom scores in patients with severe autonomic failure and OH. OH was defined as a decrease in SBP  $\geq 20$  mmHg or DBP  $\geq 10$  mmHg within 3 minutes of standing or 60° head-up tilt. Subjects were randomised to the first treatment sequence: oral atomoxetine 18 mg; oral midodrine (5 to 10 mg); placebo. The primary efficacy endpoint was the post-treatment upright SBP at 1 minute. 69 patients (55.1% male, mean age 65 years) were enrolled and dosed. Ten patients discontinued due to loss to follow-up, and were evenly distributed across treatment groups.

Midodrine significantly increased upright SBP by 12 mmHg (95% confidence interval (CI): 6 to 19;  $p < 0.001$ ) and upright DBP by 7 mmHg (95% CI: 3 to 11;  $p = 0.001$ ) versus placebo. Similarly, atomoxetine significantly increased upright SBP by 20 mmHg (95% CI: 13 to 27;  $p < 0.001$ ) and upright DBP by 11 mmHg (95% CI: 7 to 14;  $p < 0.001$ ) versus placebo.

*Kaufman et al. (1988)*

Kaufman et al. (1988);<sup>18</sup> was a randomised, single centre, double blind, cross-over study in subjects with severe OH due to autonomic failure. Following 7 days of placebo treatment, subjects received open label midodrine four times a day, titrated to effect (to a maximum of 40 mg/day). This dose was maintained for 7 days before randomisation into the double blind treatment: 0.1 mg fludrocortisone + placebo or 0.1 mg fludrocortisone + midodrine treatment for 7 days. This was followed by a second wash-out period (placebo) lasting 2 days, before cross-over for the final week. Supine and upright BP values were recorded 10 minutes after quiet recumbency and 2 minutes after standing and bodyweight was recorded daily. The study included 7 subjects.

Open label midodrine produced a statistically significant increase in upright mean arterial pressure (MAP) in 3 (42.9%) subjects and an average rise of 5.6 mmHg (range: -8 to +20). When the combination of midodrine and fludrocortisone were compared with Baseline treatment there was an average increase in upright MAP of 6.0 mmHg (range: -20 to +32). Fludrocortisone alone generally had a negative effect on upright MAP: average -1.6 mmHg (range: -33 to +23). Generally, the addition of midodrine to fludrocortisone treatment increased upright MAP (range: -2 to +15). The sponsor sub-divided the subjects into

<sup>17</sup> Ramirez, C.E. et al. Efficacy of atomoxetine versus midodrine for the treatment of orthostatic hypotension in autonomic failure. *Hypertension*, 2014; 64: 1235-1240.

<sup>18</sup> Kaufmann, H. et al. Treatment of orthostatic hypotension due to autonomic failure with a peripheral alpha-adrenergic agonist (midodrine). *Neurology*, 1988; 38; 951-956.

responders and non-responders and investigated the effect of bodyweight on MAP. They observed that bodyweight changed in a parallel manner with upright BP, increasing in responders and decreasing in non-responders ( $p < 0.05$ ) and hypothesised that midodrine works in subjects with preserved autonomic reflexes and that midodrine may increase bodyweight via volume depletion leading to worsening of OH.

*Fouad-Tarazi et al. (1995)*

Fouad-Tarazi et al. (1995);<sup>19</sup> was a blocked, double blind, randomised crossover design study in subjects with refractory OH secondary to autonomic failure. Following a 2 day single blind placebo run-in period there was a 3 to 5 day titration period with either ephedrine or midodrine (range: 2.5 mg to 10 mg) TDS, followed by a 3 to 5 day maintenance period and a 4 day wash-out period before crossover. Concomitant fludrocortisone was permitted. BP was measured in the supine position after 3 minutes of rest then in the standing position for 1 minute. Efficacy was determined during the maintenance phase of double blind treatment. Eight hospitalised patients (50% female, mean age 60.4 years) were enrolled and completed the study. The baseline drop in supine to standing SBP was 58 mmHg and DBP 22 mmHg, respectively.

*Results:* the mean maintenance dose of midodrine was 8.4 mg and 22.3 mg for ephedrine. After midodrine dosing standing SBP increased by 17 mmHg; supine SBP increased by 19 mmHg; standing DBP increased by 5 mmHg and supine DBP by 6 mmHg. The differences in standing and supine BPs were all statistically significantly superior to placebo ( $p < 0.001$ ). Midodrine also significantly increased standing pressures over ephedrine for SBP ( $p < 0.001$ ) and DBP ( $p < 0.05$ ). Patients on midodrine treatment had approximately 50% improved ability to stand in those unable to stand at Baseline (10.7%). Midodrine decreased both supine and standing heart rates compared with placebo ( $p < 0.05$  and  $p < 0.01$ , respectively).

*Vilches-Moraga et al. (2012)*

Vilches-Moraga et al. (2012);<sup>20</sup> was a prospective long-term observational open label midodrine study in an elderly population with confirmed OH with severe symptoms. Subjects were managed at a geriatrician-led specialist falls and syncope outpatient unit. Eligible subjects had a  $> 20$  mmHg SBP drop or  $> 10$  mmHg DBP drop after standing up. Patients initially received midodrine at a dose of 2.5 mg TDS and the dose was titrated in increments of 2.5 mg. A positive response to midodrine was recorded when patients reported either a significant reduction, or an abolition of their symptoms. Patients were monitored for a median length of 2.7 years. 135 patients (mean age of 84 years (range: 64 to 97), 61.5% female, 43 (31.9%) were enrolled and dosed with open label midodrine and 101 subjects completed the study.

A benefit of midodrine (improvement or abolition of symptoms) was seen across all tilt table diagnoses with a non-statistical trend for a greater proportion of patients with vasovagal syncope (92%) to report positive outcome as compared to OH (72.1%) and other diagnoses. Sustained clinical improvement was achieved in 49% persons with 2.5 mg TDS and only 4 patients required dosages above 7.5 mg TDS.

<sup>19</sup> Fouad-Tarazi, F.M. et al. Alpha sympathomimetic treatment of autonomic insufficiency with orthostatic hypotension. *Am J Med*, 1995; 99; 604-610.

<sup>20</sup> Vilches-Moraga, A. et al. Midodrine hydrochloride in the management of older adults with neurocardiogenic syncope and orthostatic hypotension: A prospective observational study. *European Geriatric Medicine*, 2012; 3: 295-298.

*Hoeldtke et al. (1998)*

In Hoeldtke et al. (1998);<sup>21</sup> the authors reported on a case series that explored the effects of oral midodrine and subcutaneous octreotide alone and in combination on the haemodynamic response to breakfast (n = 9), and standing times and BP (n = 12). In total there were 16 enrolled subjects; 13 of whom were hospitalised, 10 had PAF, 9 were male and age ranged from 50 to 79 years. Five subjects took concomitant fludrocortisone treatment. The Baseline average orthostatic decrease in SBP was reported to be  $53 \pm 6$  mmHg.

5 mg midodrine increased mean BP by 5 to 10 mmHg over 30 minutes and only partially reversed the hypotensive effects of food. Fifteen minutes after octreotide administration to midodrine pre-treated patients, the average mean blood pressure was  $115 \pm 9$  mmHg, higher ( $p = 0.0095$ ) than after octreotide given alone ( $102 \pm 7$ ). The BP after 10 mg midodrine was significantly higher ( $p = 0.005$ ) than after 5 mg midodrine, at most time points. The Baseline standing time was  $3.5 \pm 7$  minutes; 1 hour after 10 mg midodrine,  $8.4 \pm 2.7$  minutes ( $p = 0.11$ ); after octreotide,  $13.2 \pm 3.9$  minutes ( $p = 0.0034$  versus no treatment); and after both drugs,  $21.2 \pm 5.5$  minutes ( $p = 0.0002$  versus no treatment,  $p = 0.036$  versus octreotide only).

***Efficacy – other indications***

These four studies were generally small, open label and inadequately designed or lacked statistical power to detect treatment differences between midodrine and placebo/other treatments. The results from these studies provide limited supportive efficacy data for the proposed indication, except for perhaps improved quality of life and functional indices. Generally, midodrine treatments were well tolerated in the study populations, although suboptimal dosing was generally employed compared with the proposed dosing regimen for the proposed indication.

***Efficacy – pooled and meta-analyses***

Two meta-analyses were included in the submission. Parsaik et al. (2013);<sup>11</sup> included randomised controlled trials that evaluated the efficacy of midodrine versus control in patients with OH, while Izcovich et al. (2014);<sup>12</sup> included randomised controlled trials and cross-over studies that compared midodrine versus control in patients with symptomatic OH and recurrent reflex syncope. Parsaik et al. (2013) selected nine eligible studies (seven efficacy) and Izcovich et al. (2014) selected ten eligible studies for the meta-analysis.

Parsaik et al. (2013) described two studies (Low et al. (1997)<sup>13</sup> and Wright et al. (1998)<sup>9</sup>) that reported the global assessment symptoms scale, assessed by both patients and investigators, and found a consistent favourable effect of midodrine:

- Patients: mean difference of 0.70 (95% CI 0.30 to 1.09;  $p < 0.001$ ) with significant heterogeneity ( $I^2$  97 %;  $p < 0.001$ ).<sup>22</sup>
- Investigators: mean difference of 0.80 (95% CI 0.76 to 0.85;  $p < 0.001$ ) with a relatively low degree of heterogeneity ( $I^2$  0%;  $p = 1.00$ ).

Izcovich et al. (2014) showed symptom improvement with midodrine: odds ratio 3.9 (95% CI 1.8 to 8.3), risk difference 32.8% (95% CI 13.5% to 48%), number need to treat (NNT) = 3 (95% CI 2 to 7),  $I^2$  73% versus placebo (estimated 30% improvement).

<sup>21</sup> Hoeldtke, R.D. et al. Treatment of orthostatic hypotension with midodrine and octreotide. *J Clin Endocrinol Metab*, 1998; 83: 339-343.

<sup>22</sup>  $I^2$  is a statistic that describes the percentage of variation in studies that is due to heterogeneity, rather than chance.

## Safety

The clinical dossier included safety data for 11 studies relevant to the proposed indication and a further four studies with evaluable data for off-label indications and the pooled safety analysis from two meta-analyses. A total of 559 patients were exposed to midodrine in the clinical studies and 537 received midodrine within the proposed dose range. All studies were of short duration except for Vilches-Moraga et al (2012)<sup>20</sup> in which 43 elderly subjects were exposed for a mean of 2.7 years. From the meta-analyses, the mean age was approximately 53 years and females accounted for 48% of subjects. Most studies were conducted in the USA in a predominantly Caucasian population which may have implications for the generalisability of results to other ethnic populations and the role of CYP2D6 polymorphisms on midodrine metabolism.

Many AEs were pharmacologically predictable such as pilomotor reactions and urinary urgency, retention and frequency. AEs were generally mild to moderate in severity, transient, non-serious and reversible. No deaths were reported in any clinical study. Supine hypertension was the most serious adverse reaction associated with midodrine treatment. A dose-response relationship between midodrine and supine hypertension was demonstrated and the pooled risk ratio was 6.38 in Parsaik et al. (2013) and 5.31 in Izcovich et al. (2014).

Midodrine has QT liability and there is a propensity for significantly prolonged QT in some subjects.<sup>23</sup> This is supported by nonclinical studies in dogs.

There were no reports of serious skin reactions but the New Zealand Data Sheet states that *'Although a causal relationship has not been identified, there have been cases of serious skin reactions, including Stevens Johnson Syndrome, associated with the use of midodrine'*.<sup>24</sup> Stevens Johnson syndrome and other serious skin conditions have been added to the Summary of safety concerns in the risk management plan (RMP; see *'Risk management plan'* section, below).

There was a lack of data on long-term exposure to midodrine. Long-term safety data included in the submission did not comply with the minimum 12 months' duration specified in the TGA adopted EU guideline for medicinal products for long-term use.<sup>5</sup> At the request of the evaluator, the sponsor submitted an analysis of spontaneous AE reports from the Australian and overseas databases. In general, the spontaneous AE report data provided by the sponsor were consistent with the published literature and clinical trial data. Important additional AE data were identified, including Stevens-Johnson syndrome, toxic epidermal necrolysis and Torsades de pointes. The clinical evaluator identified acute respiratory failure as a potential safety signal based on a small number of deaths in the Eudravigilance database. There was a higher death rate in US FDA Adverse Event Reporting System (FAERS) patients compared to the EU-based Eudravigilance patients which may reflect a different target population and/or a more severely ill target population, and a higher initial dose regimen (10 mg three times a day). Approximately 20% of cases of death were attributed to cardiac causes in both FAERS and Eudravigilance. This supports the requirement for cardiac monitoring at baseline and on a regular basis during ongoing midodrine treatment.

<sup>23</sup> The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

<sup>24</sup> New Zealand Data Sheet for Gutron (midodrine hydrochloride) 2.5 and 5 mg tablets. Date of first approval 30 April 1992. Available from the MedSafe website.

### Clinical evaluator's recommendation

The clinical evaluator has recommended approval of midodrine for the negotiated indication:

*for 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.*

### Risk management plan

The sponsor has submitted an Australian (AUS)-RMP version 1.0 dated August 2018; data lock point (DLP) 23 April 2018 in support of this application. An updated AUS-RMP version 1.1 dated April 2019; DLP 23 April 2018 has been submitted with the response to TGA questions to incorporate the recommended changes made in the first round RMP evaluation report.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.<sup>25</sup>

**Table 3: Summary of safety concerns**

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
<b>Important identified risks</b>	Supine hypertension	Ü	-	Ü	Ü <sup>1,3</sup>
	Dysuria/urinary retention	Ü	-	Ü	Ü <sup>1,3</sup>
	Bradycardia	Ü	-	Ü	Ü <sup>1,3</sup>
	Increased intraocular pressure in patients who receive concomitant corticosteroid treatment <sup>1</sup>	Ü	-	Ü	-
	Exacerbation of symptoms in patients with thyrotoxicosis <sup>1</sup>	Ü	-	Ü	-
	Use in patients with renal impairment <sup>1</sup>	Ü	-	Ü	-
	Interaction with sympathomimetics and other vasopressor agents	Ü	-	Ü	-
	Interaction with ergot alkaloids <sup>1</sup>	Ü	-	Ü	-
	Interaction with alpha-adrenergic antagonists <sup>1</sup>	Ü	-	Ü	-

<sup>25</sup> Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
	Interaction with drug metabolised by CYP2D6	Ü	-	Ü	-
<b>Important potential risks</b>	QT interval prolongation	Ü	-	Ü	-
	Stevens-Johnson syndrome and toxic epidermal necrolysis <sup>2</sup>	Ü	-	Ü	-
	Off-label use <sup>2</sup>	Ü	-	Ü	-
	Interaction with drugs transported by peptide transporter 1 (PEPT1)	Ü	-	Ü	-
<b>Missing information</b>	Use in paediatric population	Ü	-	Ü	-
	Use in patients with hepatic impairment	Ü	-	Ü	-
	Use during pregnancy and lactation	Ü	-	Ü	-

<sup>1</sup>Updates as recommended by the RMP evaluator; <sup>2</sup>Updates as recommended by the clinical evaluator;

<sup>3</sup>Direct healthcare professional communication.

The RMP evaluator provided the following comments:

- The sponsor has proposed to monitor all the safety concerns through routine pharmacovigilance. Considering the available overseas post-authorisation experience and the sponsor's proposal to align the proposed indication to that in the EU, this is acceptable.
- The RMP evaluator required the sponsor to provide a plan to mitigate the increased risk of suffering from adverse reactions in the elderly and institutionalised patients due to unnecessary use. In response, the sponsor has proposed a letter as direct healthcare professional communication to mitigate the important identified risks of supine hypertension, dysuria/urinary retention, bradycardia.

The RMP evaluator has recommended several conditions of registration that are listed in the 'Proposed conditions of registration' section, below.

## Risk-benefit analysis

### Delegate's considerations

Midodrine has been available internationally for over 20 years as a treatment for OH. There are no products currently registered in Australia for this indication, however, treatments such as fludrocortisone are known to be used off-label. Midodrine is not currently registered in Australia but may be accessed through the SAS which suggests a clinical need that is not currently being met. The sponsor intends to register a 2.5 and a 5 mg tablet for oral use with dosing recommendations of 2.5 mg TDS titrated to response to a maximum of 10 mg TDS.

The quality evaluator was able to provide a favourable recommendation for this product. The sponsor does not have access to the international innovator's clinical study reports and has submitted literature studies for the nonclinical and clinical components of the dossier, to support the registration of midodrine. The nonclinical evaluator states that the primary data provided was insufficient to support the registration of midodrine but the

information provided raised no novel safety concerns for the use of midodrine for the intended indication and may potentially be compensated for by the long history of clinical use overseas. The clinical evaluator provided a favourable recommendation but proposed changes to the indication to reflect the submitted literature and align the wording with the EU Summary of Product Characteristics. The sponsor has accepted the clinical evaluator's changes to the proposed indication.

The sponsor included one main study, nine other studies, four studies for other indications and two meta-analyses to support the efficacy of midodrine. The studies provided evidence of a haemodynamic benefit and a symptomatic improvement with midodrine in adult patients with severe neurogenic (or autonomic) OH. The studies were generally of a short duration, but this may be acceptable given the history of use overseas.

The sponsor submitted 11 studies relevant to the proposed indication, a further four studies with evaluable safety data for off-label indications and the pooled safety analysis from two meta-analyses to support the safety of midodrine. At the request of the clinical evaluator the sponsor provided an analysis of spontaneous AE and serious adverse event data. The safety profile of midodrine is not well characterised in the submitted studies and there is a lack of long-term safety data. However, there is a long history of international experience with oral midodrine formulations. The main safety issues identified were supine hypertension, QT liability/prolongation and serious skin conditions such as Stevens Johnson syndrome. Acute respiratory failure was identified as a potential safety signal in the third round of clinical evaluation. Approximately 20% of cases of death were attributed to cardiac causes in both FAERS and Eudravigilance, that is, irrespective of target population, disease severity and initial dosing regimens. The PI contraindicates the use of midodrine in patients with severe organic heart disease, advises caution when prescribing midodrine for those with atherosclerotic disease and includes warnings on the risk of supine hypertension and QT prolongation. In addition, cardiac monitoring is undertaken at baseline and on a regular basis during ongoing midodrine treatment.

The clinical evaluator initially recommended that treatment with midodrine be restricted to patients under the care of specialists with expertise in the therapeutic area, however, the proposed indication was amended to limit the patient population to only those with severe OH due to autonomic dysfunction where other forms of treatment were inadequate. These changes, combined with the recommended cardiac monitoring and precautionary statements on supine hypertension, atherosclerotic disease and QT prolongation and the proposed risk minimisation activities in the draft RMP, may be sufficient to mitigate this risk.

### **Deficiencies of the data**

As outlined above, the nonclinical evaluator stated that the primary data provided was insufficient to support the registration of midodrine as all of the toxicology, genotoxicity; carcinogenicity and reproductive toxicity information were purely based on the foreign Product Information documents for midodrine.

The data provided to support the long-term efficacy and safety of midodrine was limited. As outlined in the draft PI, there is limited data available in the elderly population and no data available in the paediatric population.

## Proposed conditions of registration

The RMP evaluator has proposed the following conditions of registration and the sponsor has agreed to monitor the safety of midodrine in the Australian patient population through routine pharmacovigilance activities and intends to submit periodic safety update reports (PSURs), if required:

- The Midodrine SCP AUS-Risk Management Plan (RMP) (version 1.1, dated April 2019, data lock point 23 April 2018), included with submission PM-2018-02754-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- Midodrine SCP is to be included in the Black Triangle Scheme. The PI and CMI for Midodrine SCP must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

The draft PI has been updated to incorporate the black triangle symbol and mandatory text.

## Conclusion

The outstanding issues are that the clinical dossier does not provide compelling evidence of efficacy, but does provide evidence supportive of a haemodynamic benefit and symptomatic improvement in patients with severe neurogenic (or autonomic) OH. The submission lacks long-term efficacy and data from controlled studies, but there is extensive experience with midodrine overseas and midodrine appears to have an acceptable international safety profile. Subject to the advice of the Advisory Committee (see 'Advisory Committee considerations' section, below), overall the benefits likely outweigh the risks for the proposed negotiated indication.

## Proposed action

The Delegate has no reason to say, at this time, that the application for midodrine hydrochloride should not be approved for registration.

## Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Does the sponsor intend to update the summary of safety concerns to include respiratory failure as a potential safety signal?***

The sponsor notes that no safety concerns have been raised regarding respiratory failure during the evaluation of the data submitted to support this application. It is also noted that respiratory failure is not currently listed in the overseas PI's as an adverse reaction.



However, the sponsor acknowledges the Delegate's remarks regarding the absence of respiratory failure as a potential safety signal and therefore proposes that Section 4.8 of the PI be amended to include respiratory failure as post marketing adverse event reported with the use of midodrine. The proposed text is:

Respiratory, thoracic and mediastinal disorders:

Unknown: Respiratory failure

[The revised PI clean and annotated copy was provided to the TGA]

The sponsor deems this proposed update to the PI to be sufficient enough action to mitigate any potential risk and to negate the need to include respiratory failure as a potential safety signal in the RMP.

It is also noted that respiratory failure occurs with similar frequency to other adverse events that are currently not included as potential safety signals listed within the RMP but are included as AEs in the proposed PI.

### **Advisory Committee considerations<sup>26</sup>**

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

#### ***Specific advice to the Delegate***

***1. Please comment on the evidence provided in support of the efficacy of midodrine for the negotiated severe orthostatic hypotension indication.***

The ACM was of the view that the evidence provided was sufficient to demonstrate the efficacy of midodrine for the treatment of adults with severe symptomatic orthostatic hypotension due to autonomic dysfunction.

***2. Please comment on the evidence provided in support of the safety of midodrine. Does the committee have any concerns given the limited available information from published studies but extensive overseas post-authorisation experience?***

The ACM expressed concern at the lack of long term safety data for midodrine and that this should be highlighted in the PI. However, the ACM acknowledged the long history of use overseas and the current availability of the medicine in Australia through the Special Access Scheme (SAS).<sup>27</sup> The ACM was of the view that supine hypertension was the major safety concern identified by meta-analysis of AEs. The ACM considered a requirement for a boxed warning advice on this point, but instead considered that the precautionary statement in Section 4.4 should address the issues raised in the boxed warning, and this should be similarly addressed in the Consumer Medicines Information (CMI). The ACM was of the view that the number needed to harm for supine hypertension should be

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<sup>26</sup> The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.

The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

<sup>27</sup> The **Special Access Scheme (SAS)** allows certain health practitioners to access therapeutic goods (such as medicines, medical devices or biologicals) that are not included in the Australian Register of Therapeutic Goods (ARTG), for a single patient. Therapeutic goods that are not included in the ARTG (and are not otherwise exempt from being in the ARTG) are described by the TGA as 'unapproved'.

included in the PI. The ACM noted that FDA and EU post market adverse event data appeared to show a small safety signal with respect to Stevens Johnson syndrome and toxic epidermal necrolysis. The ACM was of the view that this risk should be clearly articulated in both the PI and CMI.

**3. *The indication for midodrine varies across international product information documents. What are ACM's views on the wording of the negotiated indication?***

The ACM was of the view that the indication should be amended to restrict the use of the medication to symptomatic patients only. The ACM also advised that the phrase 'corrective factors have been ruled out' should be replaced with 'exacerbating factors have been addressed', noting that this more accurately reflects the intent of treatment.

**4. *What are ACM's views on the proposed dosage instructions in the PI?***

The ACM was of the view that the dosing instructions should be amended to advise patients be started on a low dose and uptitrated on a weekly basis in 2.5 mg increments to a maximum of 10 mg TDS. The ACM advised that the current recommendation of TDS dosing should be modified to allow for BD dosing and that doses, whether TDS or BD, should not be spread evenly across the day but given in the morning and early afternoon, with the last dose being no less than 4 hours before bedtime. The ACM was of the view that the initiation of midodrine should be undertaken under close medical supervision in a controlled clinical setting. The ACM considered that the addition of 24 hour ambulatory blood pressure monitoring would be preferable to only monitoring the supine and standing blood pressure, to inform both initial diagnosis and dosing.

**5. *What are ACM's views on the risk mitigation activities? In particular, does the committee think treatment should be restricted to the care of relevant specialists?***

The ACM agreed that midodrine should be included as part of enhanced pharmacovigilance activities in the black triangle scheme, to support adverse event reporting. The ACM was of the view that initiation of midodrine should be undertaken under close medical supervision, ideally in a clinical setting, by a specialist with expertise in the treatment of severe OH.

**Conclusion**

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Vasodrine / Midodrine SCP / Midodrine ANS tablets, containing 2.5 mg; 5.0 mg of midodrine hydrochloride.

The ACM considered this product to have an overall positive benefit-risk profile for the revised indication:

*Midodrine SCP 2.5 or 5 mg tablets are indicated in adults for the treatment of severe symptomatic orthostatic hypotension due to autonomic dysfunction when exacerbating factors have been addressed and other forms of treatment remain inadequate.*

**Outcome**

Based on a review of quality, safety and efficacy, the TGA approved the registration of Midodrine SCP/Midodrine ANS/Vasodrine (midodrine hydrochloride) 2.5 mg and 5 mg tablet blister packs, indicated for:

*Midodrine SCP / Midodrine ANS / Vasodrine is indicated in adults for the treatment of severe symptomatic orthostatic hypotension due to autonomic dysfunction when exacerbating factors have been addressed and other forms of treatment remain inadequate.*

**Specific conditions of registration applying to these goods**

- Midodrine SCP/Midodrine ANS/Vasodrine (midodrine hydrochloride) are to be included in the Black Triangle Scheme. The PI and CMI for Midodrine SCP/Midodrine ANS/Vasodrine (midodrine hydrochloride) must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Midodrine SCP/Midodrine ANS/Vasodrine (midodrine hydrochloride) AUS-RMP (version 1.2, dated November 2019, DLP 23 April 2018), included with submission PM-2018-02754-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

**Attachments 1, 2 and 3. Product Information**

The PIs for Vasodrine / Midodrine SCP / Midodrine ANS approved with the submission which is described in this AusPAR is at Attachments 1, 2 and 3. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## **Therapeutic Goods Administration**

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