IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Midodrine Hydrochloride Morningside
MIDODRINE HYDROCHLORIDE
PA23142/008/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Midodrine Hydrochloride Morningside 2.5mg and 5mg tablets from Morningside Healthcare (Malta) Limited on 16th September 2022 for use in the treatment of severe orthostatic hypotension due to dysfunction of the autonomic nervous system when corrective factors have been ruled out.

This MAA is submitted via a Decentralised (DCP) procedure with article 10(1) of Directive 2001/83/EC as amended (generic application). The originator product is Midon (5 mg tablet) by Takeda Products Ireland Ltd (PA2229/008/002), registered since 26-03-1990.

With Ireland as the Reference Member State (RMS) in this DCP, Morningside Healthcare (Malta) Ltd., is applying for the Marketing Authorisations for Midrodrine 2.5 mg and 5 mg in DK, NO and SE.

No scientific advice was sought for by the applicant prior to submission of this application.

The medicinal product is applied for under "subject to medical prescription which may be renewed" in IE.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at https://www.hpra.ie/homepage/medicines

Name of the product	Midodrine Hydrochloride Morningside 2.5mg and 5mg tablets
Name(s) of the active substance(s) (INN)	MIDODRINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	C01CA17
Pharmaceutical form and strength(s)	2.5mg and 5mg tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA23142/008/001-002
Marketing Authorisation Holder	Morningside Healthcare (Malta) Limited
MRP/DCP No.	IE/H/1178/001-002/DC
Reference Member State	IE
Concerned Member State	DK NO SE

II. QUALITY ASPECTS

II.1. Introduction

This application is for Midodrine Hydrochloride Morningside 2.5mg tablets and Midodrine Hydrochloride Morningside 5mg tablets

II.2 Drug substance

The active substance is Midodrine Hydrochloride, a well-known active substance, but it is not described in the European Pharmacopoeia.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The active substance is Midodrine Hydrochloride is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The drug substance specification has been established in-house. The drug substance specification is considered adequate to control the quality in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each Midodrine Hydrochloride Morningside 2.5mg tablets contain 2.5 mg of Midodrine Hydrochloride.

Each Midodrine Hydrochloride Morningside 5 mg tablets contain 5 mg of Midodrine Hydrochloride.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
Compatibility between the active substance and the excipients is supported by stability studies. The packaging materials have shown to be suitable by acceptable stability studies.
The aim of the product development was to formulate essentially similar and bioequivalent generic formulation of GUTRON Tablets
Bioequivalence studies were performed for demonstration of bioequivalence between the generic product and the reference product GUTRON. Comparative dissolution profiles between the generic Biobatch of each strength and the reference product used in BE studies are provided and demonstrate comparability for each dissolution medium proposed by the BE-Guideline. Based on the dissolution profiles of the Bio-batches an acceptable dissolution specification has been derived.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

Batch formulae have been provided for the manufacture of the product. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines. The manufacturing process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

The excipients used in the manufacture of Midodrine Hydrochloride Morningside 2.5mg and 5 mg tablets are standard excipients in manufacturing of tablets and controlled and tested in compliance with the respective Ph. Eur. monograph. The colourant, Sunset Yellow Lake (5 mg tablets only, is specified in compliance with current foodstuff regulations and can therefore be accepted. An acceptable in-house specification is provided.

P.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form and they are and in line with ICH Q6A and Ph Eur requirements for tablets.

The tests and control limits in the specifications have been adequately justified and are considered appropriate for adequate quality control of the product. The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with relevant Ph. Eur requirements and EU legislations.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

No excipients of animal or human origin are included. The TSE/BSE free declarations from the manufacturer of all excipients are submitted.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Midodrine Hydrochloride Morningside 2.5mg tablets and Midodrine Hydrochloride Morningside 5mg tablets

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Midon on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of midodrine are well known. As midodrine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required.

III.2 Ecotoxicity/environmental risk assessment

Since Midodrine Hydrochloride Morningside 2.5 and 5 mg Tablets is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

No new nonclinical studies were performed and a nonclinical overview based on literature review was provided. This is considered acceptable for this type of generic application. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Midodrine is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Midon (5 mg tablet) marketed by Takeda Products Ireland Ltd (PA2229/008/002), registered since 26-03-1990. The reference product used in the bioequivalence study was Gutron (5 mg tablet) by Takeda GmbH Austria, registered since 06-02-1974. The choice of the reference product in the bioequivalence study has been justified.

Minor updates to the SmPC Section 4.1 and 4.2 and the PIL were carried out within this procedure to improve readability and clarify instructions for the prescriber in accordance with EMA SmPC guidance; the product information is otherwise in line with the reference.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Midrodrine Tablets 5 mg of Morningside Healthcare Ltd., UK is compared with the pharmacokinetic profile of the reference product Gutron Tablets 5 mg of Takeda GmbH, 16515 Oranienburg, Deutschland.

A biowaiver for midodrine 2.5 mg tablets (lower strength) was also submitted.

Study outline: A randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Midrodrine Tablets 5 mg of Morningside Healthcare Ltd., UK with Gutron Tablets 5 mg marketed by Takeda GmbH, 16515 Oranienburg, Deutschland in Normal, Healthy, Adult, Human Subjects under Fasting Condition.

The intra-subject variability of this study was <30% for both Cmax and AUC0-t; therefore the standard acceptance limits of 80.00-125.00% apply. The 90% confidence intervals for ln-transformed data for Cmax and AUC0-t were 97.91-117.72% and 97.97-107-34% respectively, all of which are within the acceptance limits.

Table 07 (B): The geometric mean and 90% confidence interval based on least squares mean obtained from ANOVA for the ln-transferred pharmacokinetic parameters C_{max} and AUC_{0-t} are summarized in the following table (N=28)

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	24.2119	23.6095	102.5514	97.9740	107.3427
C_{max}	29.7383	27.6992	107.3616	97.9133	117.7217

**Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.*

Based on the pharmacokinetic parameters of midrodrine, the reference tablet Gutron Tablets 5 mg marketed by Takeda GmbH and test tablet Midrodrine Tablets 5 mg of Morningside Healthcare Ltd. are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The biowaiver submitted for Midodrine 2.5 mg tablets (lower strength) met the requirements of the CHMP guidance documents.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

No additional studies investigating the pharmacokinetic effects of Midrodrine 2.5mg and 5 mg Tablets were conducted which is acceptable for this generic application.

Absorption

Midodrine taken orally is rapidly and almost completely absorbed, with a mean absolute bioavailability (as DMAE) of 93%. After the oral administration of 2.5 mg midodrine in a single dose to 12 volunteers, the mean peak concentration of unchanged midodrine is approximately 10 ng/mL and it occurs after 20-30 minutes, with a terminal plasma half-life of 0.4-0.5 hours. The mean plasma concentration of the active metabolite, DMAE, peaks in approximately 1 hour, with a plasma half-life of approximately 3 hours after the oral administration of 2.5 mg midodrine. The bioavailability of DMAE is not affected by food.

Metabolism

Thorough metabolic studies have not been conducted, but it appears that deglycination of midodrine to DMAE takes place in many tissues, and both compounds are metabolized in part by the liver. Neither midodrine nor DMAE is a substrate for monoamine oxidase. Approximately the same amount of DMAE is formed after IV and PO administration of midodrine.

The human cytochrome P450 (CYP) isoforms catalyzing the oxidation metabolism of DMAE, an active metabolite of midodrine, were studied. Recombinant human CYP2D6, 1A2 and 2C19 exhibited appreciable catalytic activity with respect to the 5'-O-demethylation of DMAE. The O-demethylase activity by the recombinant CYP2D6 was much higher than that of other CYP isoforms. Quinidine (a selective inhibitor of CYP2D6) inhibited the O-demethylation of DMAE in pooled human microsomes by 86%, while selective inhibitors for other forms of CYP did not show any appreciable effect.

Distribution

Midodrine diffuses poorly across the blood-brain barrier. Neither midodrine nor DMAE is bound to plasma proteins to any significant extent.

Elimination
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.

IV.3 Pharmacodynamics

No additional studies investigating the pharmacodynamic effects of Midrodrine 2.5mg and 5 mg Tablets were conducted which is acceptable for this generic application.

For further information see the SmPCs Section 5.1.

IV.4 Clinical Efficacy

No new Applicant-generated efficacy studies or bibliographical data were submitted in this application.

IV.5 Clinical Safety

No new Applicant-generated safety studies or bibliographical data were submitted in this application.

The bioequivalence reference product for this application, Gutron 5 mg (Takeda GmbH) has been on the EU market since 1974. Midodrine can be considered to have an established clinical safety profile.

During the pivotal bioequivalence study, both the test and reference products were well tolerated by the subjects. No death, serious adverse event, significant adverse event or adverse event was observed during the entire course of the study.

Risk Management Plan
A risk management plan was submitted, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Midodrine Hydrochloride Morningside 2.5mg and 5 mg Tablet.

Safety specification

Important identified risks	• Supine hypertension and/ or excessive hypertension upon concomitant use of sympathomimetic and other vasoconstrictive agents • Reflex Bradycardia
Important potential risks	• None
Missing information	• Use in patients with hepatic impairment

Routine pharmacovigilance and routine risk minimisation activities were proposed by the applicant, which is endorsed.
PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

This decentralised marketing authorisation application was submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended (generic application) for Midrodrine 2.5 mg and 5 mg. The originator product is Midon (5 mg tablet) by Takeda Products Ireland Ltd (PA2229/008/002), registered since 26-03-1990.

One bioequivalence study was submitted, in which the pharmacokinetic profile of the test product Midrodrine Tablets 5 mg of Morningside Healthcare Ltd., UK was compared with the pharmacokinetic profile of the reference product Gutron Tablets 5 mg of Takeda GmbH.

The biowaiver submitted for Midodrine 2.5 mg tablets (lower strength) met the requirements of the CHMP guidance documents.

The 90% confidence intervals for ln-transformed data for C_{max} and AUC_{0-t} were 97.91-117.72% and 97.97-107-34% respectively, all of which are within the acceptance limits and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Midrodrine is a well-known active substance with established efficacy and tolerability. The bioequivalence reference product, Gutron 5 mg (Takeda GmbH) has been on the EU market since 1974, midrodrine in general has been marketed for several decades. The reference product for this application, Midon (5 mg tablet) by Takeda Products Ireland Ltd., has been on the market in IE since 1990. The safety results reported in the bioequivalence study were found to be consistent with the known safety profile of Midrodrine and no other safety studies were submitted in support of this study which is acceptable.

V. OVERALL CONCLUSIONS

Midrodrine 2.5 mg and 5 mg Tablets are a generic form of Midon (5 mg tablet) by Takeda Products Ireland Ltd. Midon (5 mg tablet) by Takeda Products Ireland Ltd is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Midrodrine 2.5 mg and 5 mg Tablets can be considered bioequivalent to the reference product,and that a satisfactory risk/benefit profile has been demonstrated and therefore has granted a marketing authorisation.

VI. REVISION DATE

20.07.2027