IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Midodrine Hydrochloride 5 mg tablets
MIDODRINE HYDROCHLORIDE
PA23215/001/002

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 2.5 mg & 5 mg Tablet, from Milstein C.V on 11th February 2022 for the following indication:
Midodrine is indicated 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.

This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application for the 5mg strength of Midodrine hydrochloride. The application was submitted in accordance with Article 10(3) of Directive 2001/83/EC so called "hybrid application" for the 2.5mg strength tablet.

The application was assessed through a decentralised procedure in which the HPRA acted as RMS (reference member state) and France acted as the concerned member state (CMS) in the procedure.

Midodrine Hydrochloride 2.5 mg & 5 mg Tablets are authorised for pharmacy only supply as a prescription only medical product which may be renewed (B).

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

Name of the product	Midodrine Hydrochloride 2.5 mg & 5 mg Tablet
Name(s) of the active substance(s) (INN)	MIDODRINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	C01CA17
Pharmaceutical form and strength(s)	2.5 mg & 5 mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA23215/001/001-2
Marketing Authorisation Holder	Milstein C.V
MRP/DCP No.	IE/H/0993/001-002/DC
Reference Member State	IE
Concerned Member State	FR

II. QUALITY ASPECTS

II.1. Introduction

This application is for Midodrine Hydrochloride 2.5 mg & 5 mg Tablets.

II.2 Drug substance

The active substance is Midodrine Hydrochloride, an established active substance not described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Midodrine Hydrochloride 2.5 mg Tablets: Each tablet contains 2.5 mg of midodrine hydrochloride.
Midodrine Hydrochloride 5 mg Tablets: Each tablet contains 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.

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.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

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

All ingredients comply with corresponding Ph. Eur. monographs and are adequately controlled.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches 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 legislation for use with foodstuffs requirements.

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.

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 2.5mg & 5mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Gutron 5 mg Tablets on the European market. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of midodrine hydrochloride are well known. As midodrine hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Midodrine Hydrochloride 2.5mg & 5mg Tablet is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As midodrine hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

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

Midodrine is indicated 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.

This decentralised application for a marketing authorisation for Midodrine 2.5mg and 5mg tablets containing the active substance Midodrine hydrochloride was submitted to HPRA in accordance with Article 10(1) of Directive 2001/83/EC for the 5mg strength tablet, referred to as a 'generic' application.
The application was submitted in accordance with Article 10(3) of Directive 2001/83/EC, so called "hybrid application", for the 2.5mg tablet strength.

The EU reference product is Gutron 5mg Tablets which are marketed by Takeda Netherland B.V, in the Netherlands, registered since 30/01/1995.

The indication and posology and the overall content of the product information for this generic product are in line with that of the reference product and other recently approved Midodrine DCPs in the EU.

This medicinal product is intended for oral administration.
The submission of a bioequivalence study was applicable according to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98Rev.1/Corr**).
A bioequivalence study was performed to compare the pharmacokinetic profiles of Midodrine hydrochloride 5mg tablets versus the EU reference product Gutron 5mg Tablets and justification for a biowaiver for the lower strength, 2.5mg tablet, was submitted.

In the context of the bioequivalence study, the applicant performed an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Midodrine 5 mg tablets (Test: ChromePharma, UK) and Gutron 5 mg tablets (Reference: Takeda Netherland B.V. the Netherland) in healthy, adult subjects under fasting conditions.

Essential similarity between the test and reference products was demonstrated.

Based on the pharmacokinetic parameters of the active substance Midodrine hydrochloride the reference tablet Gutron 5mg Tablets which are marketed by Takeda Netherland B.V, in the Netherlands and test tablet 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 approach was used for the lower strength (2.5mg tablet) in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver this was considered acceptable.

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the European reference product.

IV.2 Pharmacokinetics

The pharmacokinetic profile of Midodrine hydrochloride is well established. No new data in addition to the bioequivalence study has been submitted. The pharmacokinetics of Midodrine hydrochloride have been adequately discussed by the applicant and the overview is based on published literature, supported by the clinical study.

IV.3 Pharmacodynamics

The pharmacodynamics of Midodrine hydrochloride are established and have been adequately discussed by the applicant and the overview is based on published literature.
The applicant has not submitted any new pharmacodynamic data in accordance with EC article 10.1 (a) (iii) of directive 2001/83/EC which is considered acceptable for this type of application.

IV.4 Clinical Efficacy

The efficacy of midodrine in the proposed indication is established in clinical use. No new clinical efficacy studies are provided and none are required.

For this generic application, a bioequivalence study has been submitted by the applicant for the 5mg strength of Midodrine and a biowaiver approach was used for the lower strength (2.5mg) in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver.
Midodrine 5mg film-coated tablets was compared to the European reference product Gutron 5mg Tablets which are marketed by Takeda Netherland B.V, in the Netherlands mg film-coated tablets.

An open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Midodrine 5 mg tablets (Test: ChromePharma, UK) and Gutron 5 mg tablets (Reference: Takeda Netherland B.V. the Netherland) in healthy, adult subjects under fasting conditions.

Essential similarity between the test and reference products was demonstrated.

Based on the pharmacokinetic parameters of active substance Midodrine hydrochloride the reference tablet Gutron 5 mg tablets (Reference: Takeda Netherland B.V. the Netherland) and test tablet Midodrine 5mg Film Coated Tablets 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 approach was used for the lower strength (2.5mg) in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver, a justification for the biowaiver for the 2.5mg lower strength of midodrine hydrochloride was submitted and this approach was considered acceptable.

IV.5 Clinical Safety

The overall safety profile of midodrine is established and generally known. No additional safety studies are provided which is acceptable for this application type.
The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

No new safety concerns were identified during the Bioequivalence study submitted with this application. The safety profile of midodrine hydrochloride is well established and has been adequately discussed by the applicant.
No post-marketing data is available.

Risk Management Plan
The MAH has submitted a risk management plan, version 0.2, dated 29 September 2020, 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 2.5mg and 5mg tablets. The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

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. The Marketing Authorisation Holder shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list. In case the active substance will be removed in the

future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

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

The clinical pharmacology, efficacy and safety of the active substance are well known and have been adequately discussed in the clinical overview for this type of application.

For this generic application, one bioequivalence study has been presented for the 5mg strength of Midodrine. Based on the pharmacokinetic parameters of active substance Midodrine hydrochloride, the reference tablet Gutron 5 mg tablets marketed by Takeda Netherland B.V. the Netherland was shown to be bioequivalent to the test product Midodrine 5 mg tablets ChromePharma, UK in healthy, adult subjects under fasting conditions with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver approach has been used in relation to the lower strength in line with the Note for guidance on Bioavailability-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver, this approach is considered acceptable.
There is a precedent for the acceptance of a BCS-based biowaiver in this instance and a similar approach has been accepted in other DCP procedures where midodrine generics have been successfully authorised in Europe.

The proposed excipients are considered standard for the dosage form in line with the current EU guidance.

A number of questions were raised during the assessment phase of the procedure and the applicant has provided satisfactory responses to all the points raised and has justified their approach. This is considered acceptable.

Routine risk minimisation measures and routine pharmacovigilance activities were proposed to address the known safety concerns for the active substance and this is considered acceptable.

The Applicant is requested to submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) 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.

V. OVERALL CONCLUSIONS

The active substance, midodrine hydrochloride, is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established efficacy and safety profile.

This decentralised application for a marketing authorisation for Midodrine 2.5mg and 5mg tablets was submitted to HPRA in accordance with Article 10.1 of Directive 2001/83/EC for the 5mg strength tablet and in accordance with Article 10.3 of Directive 2001/83/EC for the 2.5mg strength tablet.

Midodrine 2.5mg and 5mg tablets are a generic formulation of the European reference product, Gutron 5mg Tablets, which are marketed by Takeda Netherland B.V, in the Netherlands, registered since 30/01/1995.

The indication and posology and the overall content of the product information for this generic product are in line with that of the reference product and other recently approved Midodrine tablet DCPs in the EU. Further, the content of the SmPC has also taken account of recently authorised decentralised midodrine generics.

For this generic application, a bioequivalence study has been submitted for the 5mg strength of midodrine.
Bioequivalence has been shown to be in compliance with the CHMP guidance documents.
Further, a biowaiver approach was undertaken for the 2.5mg strength of midodrine, in line with the Note for guidance on Bioavailability and bioequivalence-CPMP/EQP/QWP/1401/98, as these applications are based on a Biopharmaceutics Classification System BCS class I biowaiver.
The overall approach was acceptable and bioequivalence has been demonstrated.

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 in this application, considered that Midodrine hydrochloride 2.5mg and 5mg tablets demonstrated adequate evidence of efficacy and safety for the approved indication, as well as a satisfactory risk/benefit profile in line with that established in the EU and has therefore granted a marketing authorisation.

VI. REVISION DATE

16.09.2026