IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Midodrine Tillomed 2.5 mg tablets
Midodrine hydrochloride
PA23169/002/001

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 Tillomed 2.5mg & 5mg tablet, from Laboratorios Tillomed Spain on 27th August 2021 for the treatment of severe orthostatic hypotension due to dysfunction of the autonomic nervous system when corrective factors have been ruled out.

This application for a marketing authorisation was submitted under Article 10(1) of Directive 2001/83/EC as amended and via the decentralised procedure whereby Ireland (IE) was the Reference Member State and France and the UK as Concerned Member States.

The authorisation was extended to additional Concern Member States, namely CY,DK, EL,FI, NO, SE, thorough Mutual Recognition Repeat Use Procedure (IE/H/0918/001-002/E/001) that positively ended on 2nd July 2023

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 Tillomed 2.5mg tablet
Name(s) of the active substance(s) (INN)	MIDODRINE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	C01CA17 Midodrine
Pharmaceutical form and strength(s)	2.5mg tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA23169/002/001
Marketing Authorisation Holder	Laboratorios Tillomed Spain
MRP/DCP No.	IE/H/0918/001/DC
Reference Member State	IE
Concerned Member State	FR UK* (initial DCP) CY,DK, EL,FI, NO, SE (Repeat use procedure) * - UK was split from DCP in April 2023

II. QUALITY ASPECTS

II.1. Introduction

This application is for Midodrine Tillomed 2.5 mg & 5 mg Tablets

II.2 Drug substance

The active substance is midodrine hydrochloride, an established active substance 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

Composition of the medicinal product

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 Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification 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 Ph. Eur./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 Tillomed 2.5 mg & 5 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Midon 2.5 mg and 5 mg tablets on the European market. No new preclinical data have been submitted.

III.5 Ecotoxicity/environmental risk assessment

Since Midodrine Tillomed 2.5 mg and 5 mg tablet 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

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.

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 (midodrine hydrochloride) marketed by Takeda Products Ireland Ltd.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product Midon tablets, MAH: Takeda Product Irelands Ltd

Bioequivalence study: 5mg strength
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Midodrine Tilomed 5 mg tablets manufactured by Emcure Pharmaceuticals Ltd, was compared with the pharmacokinetic profile of the reference product Midon 5 mg tablets, MAH: Takeda Product Irelands Ltd. Based on the pharmacokinetic parameters of active substance the reference tablet <name> marketed by <MAH> and test tablet <name> are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Biowaiver: 2.5 mg strength
The biowaiver was granted based on justification provided.
Based on the above, waiver of a bioequivalence study with the 2.5 mg strength is acceptable and the results of the bioequivalence study performed with the 5mg film-coated tablets therefore apply to the 2.5 mg film-coated tablet strength.

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

IV.2 Pharmacokinetics

Absorption
After oral administration of a dose of 2.5 mg, midodrine hydrochloride is rapidly and completely absorbed and reaches its peak plasma concentrations after approximately 20-30 minutes (Cmax approx. 0.01 mg/l, tmax < 30 min). The prodrug midodrine hydrochloride is converted in different tissues (also in liver) enzymatically into its active metabolite desglymidodrine. The absolute bioavailability of midodrine hydrochloride (and desglymidodrine) amounts to 93% after oral administration. AUC and Cmax increase proportionally to the doses in a dosage range of 2.5 – 22.5 mg. Administration with food increases the AUC by approximately 25%, and the Cmax decreases by approximately 30%. The pharmacokinetics of desglymidodrine is not affected. After oral administration of a dosage of 5 – 10 mg of midodrine hydrochloride in fasting patients with orthostatic hypertension, desglymidodrine reaches its highest plasma concentration (0.027 mg/l) approx. 1h after oral administration (tmax = 1.1 h) and after intravenous injection within a period of 60 – 120 min.

Distribution
Midodrine and desglymidodrine bind less than 30% to plasma proteins. Studies on animals
show that desglymidodrine is distributed in the target organs. The distribution of midodrine in humans has not been established, it does not appear to cross the blood-brain barrier after oral administration.

Biotransformation
This medicinal product is split into its pharmacologically active metabolite
desglymidodrine through enzymatic degradation in different tissues (including liver).

Elimination
Midodrine hydrochloride is quickly eliminated from plasma (t1/2 = 0.41 – 0.49 h), and
desglymidodrine is eliminated somewhat slowly (t1/2 = 3 h). Midodrine hydrochloride and desglymidodrine are almost completely (91%) eliminated renally within 24 hours (approx. 40 – 60% as active metabolite, 2 – 5% as non-metabolised midodrine hydrochloride, the rest as other pharmacologically inactive metabolites). The elimination of midodrine hydrochloride

or desglymidodrine through faeces is negligible. After intravenous administration, 53% of applied quantity was eliminated in the first 4 hours and 47% through urine after peroral administration. The faecal elimination is 2.1%.

IV.3 Pharmacodynamics

Mechanism of action
The alpha sympathomimetic drug midodrine hydrochloride is a prodrug, which is converted to its pharmacologically active metabolite desglymidodrine in various tissues.
Desglymidodrine is a selective alpha-1-adrenoreceptor agonist. Its effect on cardiac circulation system is mainly due to increase of systolic and diastolic blood pressure. This increase in blood pressure occurs due to arterial and venous vasoconstriction.
Midodrine hydrochloride triggers alpha receptors at the bladder, which in turn is connected with increase of tone at bladder exit and delayed emptying of the bladder

No new pharmacodynamic studies have been provided and none are required.

IV.4 Clinical Efficacy

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

IV.5 Clinical Safety

The overall safety profile of midodrine is established and generally known. No new safety studies are provided and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

The MAH has submitted a risk management plan, version 0.2, dated 28 August 2019, 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 Midorine Tillomed 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. Marketing authorisation holders 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

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.

The applicant has submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the test product Midodrine Tillomed 5mg tablet against the reference product Midon (midodrine hydrochloride) marketed by Takeda Products Ireland Ltd. in accordance with the relevant guidance. A justification for waiver of a study with the 2.5mg mg strength has been provided. No additional tests are required for this application.
The applicant has also submitted a clinical overview and summary of the evidence
demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Midodrine Tillomed 2.5mg & 5mg tablet is a generic form of Midon (midodrine hydrochloride) 2.5mg & 5mg tablets marketed by Takeda Products Ireland Ltd. Midon 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 Midodrine Tillomed 2.5mg & 5mg tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

19.03.2026.

VII. UPDATES