CBG MEB

Public Assessment Report

Scientific discussion

Midodrine HCl Brancaster 2.5 mg and 5 mg tablets

(midodrine hydrochloride)

NL/H/3123/001-002/DC

Date: 27 January 2016

This module reflects the scientific discussion for the approval of Midodrine HCl Brancaster 2.5 mg and 5 mg tablets. The procedure was finalised on 25 February 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
HCl	Hydrochloride
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NfG	Note for Guidance
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia of the United States

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Midodrine HCl Brancaster 2.5 mg and 5 mg tablets from Brancaster Pharma Limited.

The product is 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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Gutron 2.5 and 5 mg tablets (NL License RVG 16513-16514) which have been registered in the Netherlands by Takeda Nederland B.V. since 30 January 1995.

The concerned member state (CMS) involved in this procedure was the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Midodrine HCl Brancaster 2.5 mg is a white, round tablet, plain on one side with “MID” debossed above the score line and “2.5” debossed below the score line on the other side.
Midodrine HCl Brancaster 5 mg is an orange, round tablet, plain on one side with “MID” debossed above the score line and “5” debossed below the score line on the other side.

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

The tablets are packed in white, opaque, HDPE round bottles with blue polypropylene cap.

The excipients are: microcrystalline cellulose, maize starch, magnesium stearate, silica colloidal anhydrous; 5 mg only - Sunset Yellow FCF (E110).

The two strengths are not dose proportional, as there are minor differences in the proportion of the excipients.

II.2 Drug Substance

The active substance is midodrine hydrochloride, an established active substance described in the Pharmacopoeia of the United States (USP) The active substance is highly soluble in water. The substance is manufactured as a racemic mixture, containing the R and S isomer, and a crystalline form.

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.

Manufacturing process
The synthesis of midodrine hydrochloride encompasses five steps. No class 1 solvents are used. One heavy metal catalyst is used and is suitably controlled. The active substance has been adequately characterized and it has been confirmed that the racemic mixture and crystalline form I is consistently produced. The specifications of the starting materials and intermediates are acceptable.

Quality control of drug substance
The drug substance specification is in line with the USP monograph. The specification is acceptable in view of the route of synthesis and the various European guidelines and contains appropriate additional tests. Batch analytical data demonstrating compliance with the drug substance specification have been provided for five commercial-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for seven batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). Changes were noted for the first batches (begin stage), this has been adequately justified. Further, no changes or pattern is observed under any of the conditions. The proposed re-test period of 60 months can be accepted. The substance does not require any special storage condition and is not sensitive to light.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The bioequivalence study has been performed on the highest strength (5 mg) using the Dutch innovator product Gutron 5 mg as reference product. The provided dissolution profiles of the test and reference products show similarity. A biowaiver has been requested for the 2.5 mg strength. This biowaiver can be accepted, although the full requirements of the Note for Guidance (NfG) on Investigation on Bioequivalence regarding the two strengths are not met. The two strengths are manufactured using a similar process and vary slightly in amounts of excipients and active substance. However, these differences are not considered to have an effect on dissolution/availability. Hence the biowaiver can be accepted from a chemical-pharmaceutical point of view.
The tablets contain score lines but the breakability/divisibility study has not been performed according to the requirements of the Ph.Eur. Hence a statement that the products cannot be broken into equal doses is included in the SmPC.

Manufacturing process
The drug products are manufactured using a direct compression process, consisting of blending the excipients and active substance, followed by compression of tablets.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches of each strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph.Eur. requirements and Sunset Yellow FCF with in-house requirements. These specifications are acceptable and the functionality-related characteristics of the excipients have been discussed.

Quality control of drug product
The product specification includes tests for appearance, average weight, identification, dissolution, uniformity of dosage units, water content, degradation products, assay and microbiological purity. The shelf-life limits are the same as the release limits. This is considered acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three full-scale batches of the 2.5 mg strength and six batches of the 5 mg strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided of five full-scale batches stored at 25°C/60% RH (up to 36 months) and two batches at 40 °C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white HDPE bottles

with blue PP caps with foam liner and induction seal. The packaging was not fully according to the proposed packaging as the tablet count differed for some batches (30 count and 1000 count besides the proposed 100 count). Some fluctuation was observed in assay values at accelerated conditions, leading to an out of specification result and a significant change in one batch of the 2.5 mg strength. The MAH will start stability studies at intermediate conditions and accelerated conditions post approval. In the meantime, the storage restriction 'store below 25 °C' is applied. The claimed shelf-life of 36 months can be granted.

Stability data demonstrating that the product remains stable following first opening of the container for 33 days has been provided. Extrapolation calculations have been performed and the in-use period which can be granted is 8 weeks.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Midodrine HCl Brancaster 2.5 mg and 5 mg have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed to place a batch of each strength on stability at intermediate conditions (30°C/65% RH) for 12 months and accelerated conditions (40°C/75% RH) for 6 months.
- The MAH committed to place one batch of each strength on an in-use stability program (up to 8 weeks) when these batches are nearing the end of their shelf-life, in accordance with the NfG on in-use stability testing of human medicinal products.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

An ERA was triggered due to increased use. The MAH performed an ERA for the UK as worst case scenario. Using a refined Fpen of 0.00031, a PECsurfacewater of 0.0032 µg/L is obtained. As this is below the action limit of 0.01 µg/L, a further assessment is not deemed necessary.
The persistent, bioaccumulative and toxic (PBT) assessment cannot be concluded as log Kow is not available.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Gutron tablets, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Regarding the ERA, the following commitment was made:
- The MAH will initiate the log Kow study as requested for desglymidodrine in accordance with OECD TG 107, utilising the methodology prescribed under option b), at the earliest opportunity. Following receipt of this study report, the MAH commits to providing a fully updated ERA and the completed study report. The MAH fulfilled the commitment of submitting the log Kow report via variation procedure NL/H/3123/001-002/IB/001.

IV. CLINICAL ASPECTS

IV.1 Introduction

Midodrine HCl is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below. A second study report was provided on a bioequivalence study with a reference product not registered in the EU. This study was not assessed, as it has no relevance for the application.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Midodrine HCl Brancaster 5 mg (Brancaster Pharma Limited, UK) is compared with the pharmaco-kinetic profile of the reference product Gutron 5 mg tablets (Takeda Nederland B.V., NL).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH provided the following justification for a biowaiver for the lower strength:

a) midodrine hydrochloride is reported to be a BCS-class I substance (supported by in-house solubility data);
b) midodrine hydrochloride does not have a narrow therapeutic index;
c) the 2.5 mg tablets have a composition that is qualitatively the same as the 5 mg strength (other than the inclusion of the colourant in the 5 mg formulation);
d) although the strengths are not dose proportional, the 2.5 mg tablets have a composition that is quantitatively very similar to the 5 mg strength, any differences are minor;
e) the 2.5 mg tablets are manufactured by essentially the same manufacturing process as the 5 mg strength;
f) the results of in vitro dissolution tests at three different buffers (0.1 N HCl, acetate buffer (pH 4.5) and phosphate buffer (pH 6.8)), including the media intended for drug product release (0.1N HCl), obtained with the batches of the test and reference products used in the bioequivalence study show rapid dissolution i.e. ≥ 85% in 15 minutes;
g) midodrine hydrochloride has linear pharmacokinetics across the strengths from 2.5 mg to 10 mg.

All requirements for waiving bioequivalence studies as required by the current guideline on Investigations of Bioequivalence are fulfilled, and therefore a biowaiver for the 2.5 mg tablets has been granted.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy (17 males/19 females) subjects, aged 18-53 years. Each subject received a single dose (5 mg) of one of the 2 midodrine HCl formulations. The tablet was orally administered with 200 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre dose and at 0.08, 0.17, 0.25, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 4.5, 5.0 and 6.0 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-lives. Also the washout period is acceptable. Food has a slight effect on the rate and extent of absorption but this product can be taken regardless food intake. Therefore, a study under fasting conditions is justified.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 36 subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of midodrine under fasted conditions.

Treatment N=36	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	17.23 ± 3.70	17.65 ± 3.67	23.54 ± 9.25	0.33 0.17 - 1.75	--
Reference	17.79 ± 4.32	18.17 ± 4.31	25.17 ± 9.24	0.33 0.17 - 1.00	--
***Ratio (90% CI)**	0.98 (0.94 - 1.02)	--	0.92 (0.81 - 1.05)	--	--
CV (%)	10.2	--	32.8	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Midodrine HCl Brancaster 5 mg is considered bioequivalent with Gutron 5 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 HCl Brancaster.

- Summary table of safety concerns as approved in RMP

Important identified risks	– Supine hypertension leading to stroke/death – Impaired excretion of Midodrine and metabolites (in patients with impaired renal function) – The vasoconstrictor effect of Midodrine may worsen conditions that are particularly sensitive, especially those affecting blood vessels in the eye. – The sympathomimetic effects of Midodrine may worsen conditions that affect the sympathetic nervous

	system. – Worsening of orthostatic hypotension – Urinary retention – Concomitant treatment with sympathomimetics and other vasoconstrictive substances – Concomitant treatment with drugs that reduce heart rate – Concomitant treatment with drugs that increase intra-ocular pressure
Important potential risks	– Effects in heart disease – Effects in narrow angle glaucoma – Effects in proliferative diabetic retinopathy
Missing information	– Use in pregnancy and lactation – Use in hepatic impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Gutron. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Midodrine HCl Brancaster 2.5 mg and 5 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Gutron tablets. Gutron is a well-known medicinal product with an established favourable efficacy and safety profile

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Midodrine HCl Brancaster with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 February 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Environmental Risk Assessment; submission of log Kow Study Report	NL/H/3123/001-002/IB/ 001	IB	23-9-2015	23-10-2015	Approval	No
Removal of the uniformity of dosage units (by content uniformity) specification parameter of the finished product at shelf life. Removal of the reference to the tablet dimensions within the appearance specification of the finished product at release and shelf life.	NL/H/3123/001-002/IA/002/G	IA/G	6-11-2015	9-11-2015	Approval	No