COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Midodrine HCl Brancaster 10 mg tablets

(midodrine hydrochloride)

NL/H/3123/003/DC

Date: 28 April 2021

This module reflects the scientific discussion for the approval of Midodrine HCl Brancaster 10 mg tablets. The procedure was finalised on 7 January 2021. 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
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
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 10 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 hybrid application claiming essential similarity with the innovator product Gutron 5 mg tablets (NL License RVG 16514) which have been registered in the Netherlands by Takeda Nederland B.V. since 30 January 1995.

The concerned member states (CMS) involved in this procedure were Denmark, Finland, Iceland, Norway, Sweden and the United Kingdom.

This application concerns a line extension to the previously approved Midodrine HCl Brancaster 2.5 and 5 mg tablets (procedure NL/H/3123/001-002/DC; RVG 114951-114952). The first marketing authorisation was granted on 20 March 2015.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the reference product is available in a lower strength.

II. QUALITY ASPECTS

II.1 Introduction

Midodrine HCl Brancaster 10 mg is a blue, round tablet, debossed with “APO” on one side and debossed “MID” above the score line and “10” 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 aluminium/aluminium blister packs.

The excipients are microcrystalline cellulose, maize starch, magnesium stearate, silica colloidal anhydrous and brilliant blue FCF aluminium lake (E133).

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 formulation development trials were performed with the aim to obtain Midodrine 10 mg tablets with comparable dissolution profile to the reference medicinal product, bioequivalent to the reference medicinal product and meeting all physical and chemical specifications for the involved dosage form. For the 10 mg product a BCS-based biowaiver is claimed. Supportive *in vitro* dissolution data at pH 1.2, 4.5 and 6.8 have been provided for the 10 mg test product, 5 mg registered product and 5 mg reference

product, all showing a very rapid dissolution (>85% in 15 minutes) in all three media. For the final conclusions on the acceptability of the BCS-based biowaiver, reference is made to the clinical assessment. Sufficient information has been provided on the manufacturing process development. Standard manufacturing process (direct compression) is involved. The proposed process for the 10 mg strength is very similar to the process already approved for 5 mg strength. The differences have been indicated and explained.
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 product is manufactured using conventional manufacturing techniques. The manufacturing process involves blending of the active material and excipients, followed by tabletting. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches.

Control of excipients
The excipients comply with Ph.Eur. requirements and Brilliant blue FCF aluminium lake 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.
The analytical procedures used for the 10 mg product are the same as those authorised for the 2.5 mg and 5 mg strengths. Batch analysis results for the four batches packed in the HDPE bottle and for two batches in the intended commercial packaging (Al-Al blister) have been provided. The presented results demonstrate compliance with the drug product specification.

Stability of drug product
Stability data on several production batches of the product packed in HDPE bottles have been provided that were stored at 25°C/60% RH (5 batches; 36 months), 30°C/65% RH (4 batches; 12 months) and 40°C/75% RH (2 batches; 6 months). For the product packed in the commercial blister Al-Al pack stability data on two production scale batches have been provided stored at 25°C/60% RH (3 months), 30°C/65% RH (3 months) and 40°C/75% RH (3 months). The conditions used in the stability studies are according to the ICH stability guideline. The product meets the proposed shelf-life specification at all time-points and under all tested storage conditions. Except for an increase in water content, no clear trends are observed. The available stability results for the batches packed in Al-Al blisters are comparable to the results of the batches packed in HDPE bottles. Overall, the claimed shelf-life of 3 years with storage condition “Store below 30°C” is justified. The shelf-life and storage conditions are the same as authorised for the 2.5 mg and 5 mg products.

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. No following post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

As the proposed line extension of Midodrine Brancaster is not considered to lead to an increase in environmental exposure of the compound, due to substitution of existing midodrine products, and as, in addition, an ERA is already in place for the lower strengths, no further actions are required.

III.2 Discussion on the non-clinical aspects

This product is a hybrid 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.

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.

The previously submitted bioequivalence study with the 5 mg strength showed bioequivalence of Midodrine Brancaster 5 mg to Gutron 5 mg. Midodrine displays linear kinetics over the therapeutic dose range (2.5 to 10 mg). The MAH is requesting a line extension to the 10 mg strength based on a biowaiver for an additional strength.

IV.2 Pharmacokinetics

Biowaiver

The overall submitted data to support that there are no issues expected regarding similarity in bioequivalence and bioavailability can be considered as:

- Midodrine is a BCS Class I drug, i.e. highly soluble and highly permeable. For such drug compounds the risk of bioavailability problems is low.
- Regarding the biowaiver for the additional strength, the MAH manufactured a dose proportional 10 mg formulation, and showed that dissolution at pH 1.2, 4.5 and 6.8 are similar (i.e. >85% within 15 min) with the 5 mg reference Gutron tablet and the 10 mg to be marketed formulation.
- Regarding the BCS based biowaiver, the MAH showed that dissolution at pH 1.2, 4.5 and 6.8 are similar (i.e. >85% within 15 min) with the 5 mg reference Gutron tablet, 2 x 5 mg reference Gutron tablets and the 10 mg to be marketed formulation. None contain excipients which may affect absorption. Although a BCS based biowaiver can be applied without any bioequivalence data, for the 5 mg tablet an *in vivo* bioequivalence has been submitted before, showing bioequivalence between the 5 mg reference Gutron tablet and the 5 mg test tablet, supporting that there are no bioavailability issues regarding the excipients.
- For a 10 mg dose, earlier 2 x 5 mg tablets were administered. The submitted data showed that a similar bioavailability can be expected between 2 x 5 mg tablets and 1 x 10 mg tablets.

The totality of the compelling data shows that for the 10 mg strength a similar bioequivalence/bioavailability can be expected compared to Gutron 5 mg tablets and the already marketed 5 mg formulation. In conclusion, the results of the bioequivalence study with the 5 mg formulation can be extrapolated to the 10 mg strength.

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	None
Important potential risks	None
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 results of the bioequivalence study with the 5 mg formulation could be extrapolated to the 10 mg strength. Therefore, the requested biowaiver for the 10 mg formulation is acceptable. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The submitted readability testing is the same as the one which was attached for the 2.5 mg and 5 mg strengths. According to the MAH, there are no changes to the layout or critical content for Midodrine 10 mg tablets that uses the same combined Patient Leaflet (PL) that was approved during the originator procedure. This is agreed and no further testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Midodrine HCl Brancaster 10 mg tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Gutron tablets. Gutron is a well-known medicinal product with an established favourable efficacy and safety profile. In addition, Midodrine HCl Brancaster 10 mg tablets is an approvable line extension to Midodrine HCl Brancaster 2.5 mg and 5 mg tablets.

A biowaiver has been granted.

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 7 January 2021.

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