

Public Assessment Report Scientific discussion

Midodrin Evolan (midodrine hydrochloride)

Asp no: 2016-0136, 2016-0137

This module reflects the scientific discussion for the approval of Midodrin Evolan. The procedure was finalised on 2017-05-12. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

The application for Midodrin Evolan, 2.5 mg, tablet, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC and Midodrin Evolan, 5 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Evolan Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Gutron 5 mg, tabletten authorised in the NL since 1995, with Takeda Nederland bv as marketing authorisation holder.

The reference product used in the bioequivalence study is Gutron, 5 mg, tabletten from NL with Takeda Nederland bv as marketing authorisation holder.

The active substance is considered a new active substance in Sweden.

The active substance is midodrine hydrochloride (the active metabolite, de-glymidodrine (desglymidodrine) is a selective α 1-adrenoceptor agonist and increases blood pressure via both arterial and venous vasoconstriction).

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

The active substance of Midodrin Evolan is considered a new active substance in Sweden. The product is essentially similar and refer to a product approved based on a full application with regard to non-clinical data, no further such data have been submitted or are considered necessary and an overview based on literature data is thus sufficient.

There are deficiencies in the nonclinical overview and data on genotoxicity and carcinogenicity has e.g. not been found by the applicant and are thus not presented. However, information given in the suggested SmPC regarding genotoxicity, carcinogenicity and reproductive toxicity have been updated to be in line with the information given in the SmPC for the reference product. Other deficiencies are considered to be overruled by the long clinical experience and section 4.6 and 5.3 of the SmPC are considered to contain all relevant information and are in line with the SmPC of the reference product. The deficiencies in the nonclinical overview are therefore considered acceptable.

III.2 Ecotoxicity/environmental risk assessment

The applicant has not submitted a proper ERA but only refers to Midodrin Evolan being a generic product of the reference product Gutron which according to the applicant is not known for its environmental risks.

Usually a generic product is not expected to increase the use of a drug on the market. However, since no products containing midodrine is available on the Swedish market this is not true for Midodrin Evolan. The applicant is therefore requested to submit an ERA on midodrine according to present guidelines.

The Applicant has committed to submit a variation to add an ERA within one year after approval of the Marketing Authorisation, which is considered to be acceptable.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 46 healthy volunteers, comparing Midodrin Evolan, 5 mg, tablets with Gutron, 5 mg, tablets under fasting conditions. The study was conducted at Algorithme Pharma Inc, Mount-Royal Quebec, Canada between 2015-08-20 and 2015-09-07. Blood samples were collected pre-dose and up to 6 hours post-dose. The study design is considered acceptable. Plasma concentrations of midodrine were determined with an adequately validated LC/MS/MS method.

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean (CV%), $t_{\max}$ median, range) for midodrine, n=45.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	20.831 (17.3)	23.676 (27.9)	0.50 0.25-1.75
Reference	20.619 (17.9)	22.488 (32.6)	0.50 0.25-1.03
*Ratio (90% CI)	101.06 (98.57-103.61)	106.53 (97.57-116.32)	-
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 plasma concentration			

**calculated based on ln-transformed data*

Based on the submitted bioequivalence study, Midodrin Evolan 5 mg tablet is considered bioequivalent with Gutron 5 mg tablet. From a pharmacokinetic point of view, absence of studies with the additional strength of 2.5 mg is acceptable, as the pharmacokinetics of midodrine is linear between 2.5 mg and 22.5 mg.

IV.2 Pharmacodynamics/Clinical efficacy/Clinical safety

Neurogenic orthostatic hypotension (nOH) results from failure of the autonomic nervous system (ANS) to regulate blood pressure in response to postural change, due to an inadequate release of norepinephrine (NE). Orthostatic hypotension is a severely disabling manifestation of generalised autonomic failure.

Midodrine is an inactive prodrug which, following oral or intravenous administration, undergoes slow enzymatic hydrolysis in the systemic circulation to release the pharmacologically active metabolite, de-glymidodrine (desglymidodrine). Desglymidodrine is a selective α_1 -adrenoceptor agonist and increases blood pressure via both arterial and venous vasoconstriction [McClellan et al 1998, McTavish et al 1989]. Administration of midodrine results in a rise in standing, sitting, and supine systolic and diastolic blood pressure in patients with orthostatic hypotension.

The active substance of Midodrin Evolan is considered a new active substance in Sweden. The product is essentially similar and refer to a product approved based on a full application with regard to clinical efficacy and safety data. No efficacy/safety clinical studies have been performed with the product. The approach with a clinical overview based on literature data was considered sufficient.

Concerns were initially raised on the summary of efficacy and safety data which needed to be strengthened. The risk for supine hypertension (e.g. during the night) is of special concern and the distribution of the doses (three times a day) needs to be considered. An update of the company's clinical overview was made including e.g. an article on longer-term safety data. The product information was revised with a more comprehensive description of dosing of midodrin as well as better rationales for the proposed contraindications, warnings, and interactions were.

Section 4.2 recommends a starting dose of 2.5 mg three times daily. Depending on the individual response to treatment the dose can be increased to maximum 10 mg three times daily. The blood pressure should be carefully monitored after each increase in dose. To optimise the dosing schedule, a 24-hour blood pressure monitoring can be considered. The last daily dose can be lower than the two previous doses during the same day and it should be taken at least 4 hours before going to bed to minimise the risk for supine hypertension.

IV.3 Risk Management Plans

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 Midodrin Evolan.

Safety specification

Summary table of safety concerns in RMP ver 02 (signed off on November 23, 2016)

Important identified risks	Reflex Bradycardia Urinary retention Supine hypertension
Important potential risks	Atherosclerotic complications
Missing information	Use in patients with hepatic impairment Use during pregnancy and lactation, effects on fertility

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly and the RMP is considered acceptable.

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.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Midodrin Evolan, 2.5 mg and 5 mg, tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

The Applicant has committed to submit a variation to add an ERA within one year from the approval of the Marketing Authorisation.

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Midodrin Evolan, 2.5 mg and 5 mg, tablet was approved in the national procedure on 2017-05-12.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)