LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pyridostigmin Orifarm
(pyridostigmine bromide)

Asp no: 2022-0192

This module reflects the scientific discussion for the approval of Pyridostigmin Orifarm. The procedure was finalised on 2023-02-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Pyridostigmin Orifarm, 60 mg, Coated tablet.

The active substance is pyridostigmine bromide, pyridostigmine. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Pyridostigmin Orifarm, 60 mg, Coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant Orifarm Healthcare A/S 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 Mestinon 60 mg dragerade tabletter, authorised in Sweden since 1955, with Meda AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Mestinon 60 mg coated tablet, from Finland with Meda Oy as marketing authorisation holder.

Potential similarity with orphan medicinal products
Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Pyridostigmin Orifarm is considered **not similar** (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Soliris or Vyvgart. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Soliris or Vyvgart in the treatment of *Myasthenia gravis*, does not prevent the granting of the marketing authorisation of Pyridostigmin Orifarm. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of pyridostigmine bromide are well known. As pyridostigmine bromide is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Pyridostigmin Orifarm is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Pyridostigmin Orifarm from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Pyridostigmin Orifarm with the reference product Mestinon.

Pharmacokinetic properties of the active substance
Absorption: Pyridostigmine has an oral bioavailability of 22-25 %. Following an oral dose of 60 mg maximal plasma concentrations occur at approximately 1-2 hours.

The bioavailability of pyridostigmine is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. The time to reach the peak plasma concentration is delayed by about 90 minutes by the ingestion of food, although the area under the plasma concentration-time curve is unaffected.

Linearity: Pyridostigmine follows approximately linear kinetics, with a direct correlation between the dose and plasma AUC.

Elimination: The terminal half-life is 3- 4 hours.

Study PYRI4521/PRO-00
Methods
This was a single-dose, two-way crossover study conducted in 38 healthy volunteers, comparing Pyridostigmin Orifarm, 60 mg, coated table with Mestinon, 60 mg, coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of pyridostigmine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2021-08-28 and 2021-09-11.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for pyridostigmine, n=38.

Treatment	AUC_{0-t} xg*h/ml	C_{max} xg/ml	t_{max} h
Test	**114.771 ±36.227**	**22.350 ± 8.144**	**2.00 (0.75- 5.00)**
Reference	**109.976 ±38.184**	**22.636 ± 9.164**	**1.75 (0.50- 4.00)**
***Ratio (90% CI)**	**105.52 (96.36- 115.55)**	**100.03 (91.62- 109.21)**	**-**

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*

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%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical method was adequately validated.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Pyridostigmin Orifarm.

Safety specification

The MAH has submitted the version 1.0 RMP dated 2022-02-14 and proposed the following summary safety concerns:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

The Applicant has proposed no safety concerns which is accepted. Given the fact the pyridostigmin products are well characterized, have been on the market for almost 70 years, it is acceptable to have no remaining important risks.

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 submitted Risk Management Plan, version 1.0 signed 2022-02-14 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 Swedish MPA;
- 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Pyridostigmin Meda 60 mg überzogene Tabletten, SI/H/0221/001 (former DE/H/5097/001/DC) regarding content and Kaliumklorid Orifarm 750 mg Depottabletter, DK/H/2347/001 regarding layout.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Pyridostigmin Orifarm, is found adequate. There are no objections to approval of Pyridostigmin Orifarm, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

Pyridostigmin Orifarm, 60 mg, Coated tablet was approved in the national procedure on 2023-02-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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