LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Propiomazin Orifarm
(propiomazine maleate, propiomazine)

2020-0203

This module reflects the scientific discussion for the approval of Propiomazin Orifarm. The procedure was finalised on 2020-12-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Propiomazin Orifarm, 25 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orifarm Generics 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 Propavan, 25 mg, tablet, authorised in SE since 1960, with Sanofi AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Propavan, 25 mg, tablet, from SE with Sanofi AB as marketing authorisation holder.

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/EC 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

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study (009-19) comparing propiomazine with the reference product Propavan.

Pharmacokinetic properties of the active substance

Absorption: Propiomazine has an oral bioavailability of 30-40 %. Following an oral dose of propiomazine maximal plasma concentrations occur at approximately 1-2 hours.

Elimination: The terminal half-life is 8 hours.

Study 009-19 (Pivotal study)

Methods

This was a randomised, two-treatment, four-period, two-sequence single-dose, fully replicate crossover study conducted in 80 healthy volunteers, comparing propiomazine, 25 mg, tablets with Propavan, 25 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of propimazine, R-propiomazine, S-propiomazine 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 2019-07-17 and 2019-11-16.

Results

The results from the pharmacokinetic and statistical analysis are presented in tables below.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for R-propiomazine.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test[1]	**21946.36 ± 13710.39**	**7445.83 ± 5676.69**	**1.25 (0.75-4.00)**
Reference[2]	**22774.46 ± 16553.95**	**7112.02 ± 4932.05**	**1.25 (0.75-3.00)**
***Ratio (90% CI)**	**98.92 (93.22-104.97)**	**103.07 (95.16-111.64)**	**-**
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*

[1] N=156

[2] N=157

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for S-propiomazine.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test[1]	**40959.90 ± 22917.04**	**11290.51 ± 7408.68**	**1.25 (0.75-4.00)**
Reference[2]	**42124.68 ± 26699.76**	**10680.96 ± 6213.60**	**1.50 (0.75-4.00)**
***Ratio (90% CI)**	**98.81 (93.78-104.10)**	**103.63 (96.86-110.87)**	**-**
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*
[1] N=156
[2] N=157

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for propiomazine.

Treatment	AUC_{0-t} pg*h/ml	C_{max} pg/ml	t_{max} h
Test[1]	**59728.46 ± 33759.63**	**16845.44 ± 10898.91**	**1.25 (0.75-4.00)**
Reference[2]	**61416.39 ± 39061.24**	**16033.50 ± 9344.87**	**1.25 (0.75-4.00)**
***Ratio (90% CI)**	**98.50 (93.43-103.83)**	**103.16 (96.30-110.51)**	**-**
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*
[1] N=156
[2] N=157

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 % for R-propiomazine, S-propiomazine and propiomazine.

Discussion and overall conclusion

The bioequivalence study 009-19 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 methods were adequately validated.

Based on the submitted pivotal bioequivalence study (009-19), Propiomazine Orifarm is considered bioequivalent with Propavan.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Propiomazin Orifarm.

Safety specification

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

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 10 Feb 2020 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 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 (PIL) has been performed on the basis of a bridging report making reference to Circadin 2 mg prolonged-release tablets (EMEA/H/C/000695) regarding the content and on the product Kaliumklorid Orifarm 750 mg depottabletter (DK/H/2347/001) concerning 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, Propiomazin Orifarm, is found adequate. There are no objections to approval of Propiomazin 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 application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

Propiomazin Orifarm, 25 mg, film-coated tablet, was approved in the national procedure on 2020-12-29.

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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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