LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report

# Scientific discussion

# Alimemazin Orifarm (alimemazine)

# Asp no: 2016-1816

**This module reflects the scientific discussion for the approval of Alimemazin Orifarm. The procedure was finalised on 2018-06-01. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

The application for Alimemazin Orifarm 40 mg/ml oral drops, solution, 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 Theralen 40 mg/ml oral drops, solution authorised in Sweden since 1963, 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

Given the differences in composition of Alimemazine Orifarm and the reference product Theralen, a biowaiver was not accepted by the MPA. A bioequivalence study was therefore conducted.

Study ALIM3917

*Methods*

This was a single-dose, two-way crossover study conducted in healthy volunteers, comparing Alimemazine Orifarm, 40 mg/ ml, oral drops solution with Theralen, 40 mg/ml, oral drops solution under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of alimemazine were determined with a validated 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 15 Oct 2017 and 25 Oct 2017.

*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 alimemazine.**

| Treatment | $AUC_{0-t}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **16404 ± 7097** | **1805 ± 923** | **2.50 1.50-4.50** |
| **Reference** | **15872 ± 7181** | **1810 ± 762** | **2.50 1.50-5.00** |
| ***Ratio (90% CI)** | **100.87 (93.47-108.86)** | **96.24 (86.43-107.16)** | **-** |

**$AUC_{0-t}$** 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.

Bioequivalence between Alimemazine Orifarm 40 mg/ml oral drops and Theralen 40 mg/ml oral drops has been sufficiently demonstrated.

## 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 Alimemazin Orifarm.

Safety specification

The company has provided an updated summary of safety concerns during the procedure. The list is now acceptable.

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Neuroleptic malignant syndrome (NMS)<br>• Cardiac disorders inclusive prolonged QT interval and cardiac arrhythmias |
| 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 RMP is approved

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

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 Alfonac, SE/H/1142/01/DC. 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, Alimemazin Orifarm, is found adequate. There are no objections to approval of Alimemazin 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

Alimemazin Orifarm 40 mg/ml oral drops, solution, was approved in the national procedure on 2018-06-01.

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SWEDISH MEDICAL PRODUCTS AGENCY

# 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)

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