LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Alimemazin Evolan
(alimemazine tartrate)

SE/H/1808/01/MR

This module reflects the scientific discussion for the approval of Alimemazin Evolan. The procedure was finalised on 2018-01-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Alimemazin Evolan, 20 mg, capsule, hard, is a hybrid application made according to Article 10(3) 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 Theralen, 5 mg, film-coated tablet authorised in SE since 1960, with Sanofi AB as marketing authorisation holder. The reference product used in the bioequivalence study is Theralen, 5 mg, film-coated 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

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing 1 capsule of 20 mg of Alimemazine Evolan (test) with 4 tablets of 5 mg of Theralen (reference) under fasting conditions. The study was conducted between 26/09/2016 and 13/10/2016. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of alimemazine were determined with an adequately validated LC/MS/MS method.

The results are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for alimemazine, n=25.

Treatment	**AUC_{0-t}** **ng*h/ml**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	**55.75 ± 23.90**	**6.15 ± 2.13**	**2.50** **1.00-4.50**
Reference	**52.29 ± 20.16**	**5.68 ± 1.93**	**2.50** **1.50-5.00**
***Ratio (90% CI)**	**106.87** **(99.26-115.06)**	**108.53** **(100.93-116.70)**	**-**
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%.

Conclusion: Bioequivalence between Alimemazin Evolan 20 mg capsule and Theralen 4x5 mg tablets was satisfactorily 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 Evolan.

Safety specification

Summary table of safety concerns as approved in RMP

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Epilepsy and seizures • Cardiovascular diseases/QT prolongation • Elderly and patients with dementia
Important potential risks	• Interaction with other medicinal products • Pregnancy, lactation and fertility
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 Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Epilepsy and seizures		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To assess the frequency of cases concerning epilepsy and seizures, and to assess the need to modify the risk/benefit profile for the product.

Cardiovascular diseases/QT prolongation		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To assess the frequency of cases concerning cardiovascular diseases/QT prolongation, and to assess the need to modify the risk/benefit profile for the product.

Elderly and patients with dementia		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To assess the frequency of cases concerning elderly and patients with dementia, and to assess the need to modify the risk/benefit profile for the product.

Interaction with other medicinal products		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To assess the frequency of cases concerning interaction with other medicinal products, and to assess the

Interaction with other medicinal products		
		need to modify the risk/benefit profile for the product.

Pregnancy, lactation and fertility		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To assess the frequency of cases concerning pregnancy, lactation and fertility, and to assess the need to modify the risk/benefit profile for the product.

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

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 Portuguese.
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 Alimemazin Evolan, 20 mg, capsule, hard is 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 Evolan, 20 mg, capsule, hard was approved in the national procedure on 2018-01-12.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1808/01/MR	Initial Mutual Recognition Procedure	Yes	26th of June 2018	Approval	N/A
SE/H/1808/01/II/04	The reference product Theralen 5 mg tablets has been withdrawn by its MA holder Sanofi AB and the Swedish MPA has requested that Alimemazin Evolan 20 mg capsule, hard is updated in accordance with Theralen 40 mg/ml oral drops, which belongs to the same Global MA as Theralen 5 mg tablets. Indication "*Anxiety due to alcoholism and narcomania*" has been removed, and indication "*Sleep disorders in adult*" has been modified to "*Short-term treatment of sleep disorders in adults*".	Yes	10th of March 2023	Approval	The implemented changes are summarized in the column for "Scope". Furthermore, additional changes of the product information have been made in order to achieve harmonized safety information for alimemazine products.

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

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