LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Klorzoxazon Evolan
(chlorzoxazone)

Asp no 2018-1268

This module reflects the scientific discussion for the approval of Klorzoxazon Evolan. The procedure was finalised on 2019-11-08. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

The application for Klorzoxazon Evolan, 250 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 Paraflex, 250 mg, tablet, authorised in SE since 1960, with BioPhausia AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Paraflex, 250 mg, tablet from SE with BioPhausia 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 comparing Klorzoxazon Evolan, 250 mg, tablet with the reference product Paraflex, 250 mg, tablet.

Pharmacokinetic properties of the active substance
Absorption: Chlorzoxazone is completely absorbed and the maximal plasma concentrations occur at approximately 1-2 hours.

The pharmacokinetics of chlorzoxazone is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Elimination: Chlorzoxazone is almost exclusively metabolized by CYP2E1 to 6-hydroxychlorzoxazone and is eliminated in the urine primarily in a conjugated form as glucuronide. The terminal half-life is about 1 hour.

Study BE/CHZ-013-03-2018
Methods
This was an open-label, randomized, two-period, two-way crossover single-dose study conducted in 28 healthy volunteers. After overnight fast two tablets of either Klorzoxazon Evolan, 250 mg or Paraflex, 250 mg was administered. Blood samples for concentration analysis were collected pre-dose and up to 10 hours post-dose. Plasma concentrations of chlorzoxazone were determined with an HPLC-UV method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2018-08-20 and 2018-09-04.

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 chlorzoxazone, n=28.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**23.75 ± 9.59**	**7.25 ± 2.46**	**1.25 (0.50 – 4.00)**
Reference	**23.94 ± 9.35**	**8.19 ± 3.54**	**1.38 (0.75 – 2.50)**
***Ratio (90% CI)**	**99.07 (93.80 – 104.62)**	**92.35 (84.09 – 101.42)**	**-**
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 not fully 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.

The applicant was asked to discuss how the study with 500 mg (2 x 250 mg) can be extrapolated to 250 mg tablets by showing linearity between these two strengths. The applicant searched in the literature showing results of AUC measured in subjects that was dosed with 250 mg and 500 mg chlorzoxazone. A linearity evaluation cannot be performed between several independent studies. Although a certain linearity cannot be evaluated, there is a tendency showing that a non-linearity is not of concern. Also, a dose of 500 mg is within the recommended dose regimen. The bioequivalence study conducted with 500 mg (2 x 250 mg) is justified.

Based on the submitted bioequivalence study, Klorzoxazon Evolan is considered bioequivalent with Paraflex.

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 Klorzoxazon Evolan.

Safety specification
The MAH has submitted an amended RMP version 0.2 for Klorzoxazon Evolan dated 19 June 2019, with the following proposed summary of safety concerns (RMP Module SVIII):

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 0.2 (Klorzoxazon Evolan) dated 19 June 2019 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

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.

For the layout a bridging report making reference to Natriumklorid Evolan 500 mg capsules (Asp no 2014-0066, MAno 50769) has been performed. 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, Klorzoxazon Evolan, is found adequate. There are no objections to approval of Klorzoxazon Evolan, 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

Klorzoxazon Evolan, 250 mg, tablet, was approved in the national procedure on 2019-11-08.

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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

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se