LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Klorzoxazon Orifarm
(chlorzoxazone)

Asp no: 2018-1200

This module reflects the scientific discussion for the approval of Klorzoxazon Orifarm. The procedure was finalised on 2019-11-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Klorzoxazon Orifarm, 250 mg, 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 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 two bioequivalence studies, one pilot study and one pivotal study comparing Klorzoxazon Orifarm with the reference product Paraflex. The pilot study was performed to calculate intra subject variability (CV%), to estimate pivotal study sample size, to assess PK parameters in order to optimize full trial sampling time and to calculate relative bioavailability of the test oral formulation of Klorzoxazon Orifarm 250 mg tablets compared to two oral formulations; herein the reference product Paraflex 250 mg tablets.

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 metabolised by CYP2E1 to 6-hydroxychlorzozazone and is eliminated in the urine primarily in a conjugated form as glucuronide. The terminal half-life is about 1 hour.

Study (Pilot Study)
Methods
This was a single-dose, three-periods, three-treatments, six-sequences, crossover relative bioavailability pilot study conducted in 18 healthy volunteers, comparing Klorzoxazon Orifarm, 250 mg, tablets with two products; herein the reference product Paraflex, 250 mg, tablets (reference 1) under fasting conditions. Blood samples for concentration analysis were collected pre-dose (-1.00) and up to 12 hours post-dose. Plasma concentrations of chlorzoxazone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}.

Results
The study results showed that the relative bioavailability ratios of $AUC_{0\rightarrow last,}$ $AUC_{0\rightarrow inf}$ and C_{max} for chlorzoxazone for test formulation to the reference 1 formulation were 95.84 (90% CI 86.75-105.89 %), 95.89 (90% CI 86.85-105.87) and 93.72 (90% CI 77.71-113.03 %) respectively, Intra subject variability (CV %) of $AUC_{0\rightarrow last}$, $AUC_{0\rightarrow inf}$ and C_{max} were 16.65, 16.54 and 31.85 respectively.

Study (Pivotal Study)

Methods

This was a single-dose, four-periods, two-treatments, two-sequences, fully replicated, crossover bioequivalence study conducted in 32 healthy volunteers, comparing Klorzoxazon Orifarm, 250 mg, tablets with Paraflex, 250 mg, tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose (-1.00) and up to 10 hours post-dose. Plasma concentrations of chlorzoxazone were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}.

Results

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

Table 1. Result of the pivotal bioequivalence study. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for chlorzoxazone, n=32.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**11182.087 ± 4154.143**	**5542.761 ± 2136.708**	**1.67 (0.50 – 5.00)**
Reference	**10876.263 ± 4118.770**	**4983.778 ± 2123.786**	**1.67 (0.50 – 5.00)**
***Ratio (90% CI)**	**102.88 (97.20 – 108.89)**	**112.20 (100.61 – 125.13)**	**-**
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} 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 C_{max}, the ratio of the test and reference product fell within the widened acceptance range of 76.92-129.99 %.

Discussion and overall conclusion

The widened acceptance range for C_{max} is acceptable as the applicant performed a fully replicated, cross-over study showing that the within-subject variability for C_{max} of the reference compound is >30 %. The widened interval was prospectively specified in the protocol. The intra-subject variability is not a result of outliers. The clinical justification for widened acceptance range is acceptable.

The pivotal 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 methods were adequately validated.

Based on the submitted pivotal bioequivalence study, Chlorzoxazone 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 Orifarm.

Safety specification

Table 1. Summary of safety concerns

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

In the day 111 response, the MAH submitted an updated version of the RMP, due to QPPV has been changed. The Risk Management Plan, version 1.1 signed 24.06.2019 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

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 Methocarbamol 750 mg filmcoated tablets, UK/H/1876/001 for content and Prednisolon Alternova 2,5 mg; 5 mg; 10 mg tablets, national variation no. (Dnr): 2121:2012/37638 for the 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, Klorzoxazon Orifarm, is found adequate. There are no objections to approval of Klorzoxazon 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

Klorzoxazon Orifarm, 250 mg, Tablet, was approved in the national procedure on 2019-11-15.

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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)

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