LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Delipam
(oxazepam)

SE/H/2272/01-03/DC

This module reflects the scientific discussion for the approval of Delipam. The procedure was finalised on 2023-05-03. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Delipam, 5 mg, 10 mg, 15 mg, tablet.

The active substance is oxazepam. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Delipam, 5 mg, 10 mg, 15 mg, tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Sobril, 15 mg, tablet authorised in SE since 1966, with Pfizer AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Sobril, 15 mg, tablet from IS with Pfizer ApS as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS NO: Sobril, 5 mg, tablet authorised in SE since 1988, with Pfizer AB as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of oxazepam are well known. As oxazepam is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Delipam is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Delipam from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study, comparing the applied Oxazepam 15 mg tablet with the reference product Sobril 15 mg tablet.

Pharmacokinetic properties of the active substance
Following oral administration maximal plasma concentrations occur at approximately 2 hours. There are no restrictions with respect to food in the SmPC of the originator.

Oxazepam is eliminated quickly, primarily via the kidneys, with a half-life of approximately 10 hours. There are no active metabolites.

Study OXAZ3021
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers (32 completed both study periods), comparing Oxazepam 15 mg tablet with Sobril, 15 mg tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of oxazepam 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 15 Oct 2021 and 11 Nov 2021.

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 oxazepam, n=32.

Treatment	AUC_{0-t} xg*h/ml	C_{max} xg/ml	t_{max} h
Test	**1203 ± 844**	**161 ± 61**	**2.33 (0.75 - 5.00)**
Reference	**1193 ± 669**	**145 ± 47**	**2.17 (1.33 - 5.00)**
***Ratio (90% CI)**	**98.11 (93.85 – 102.57)**	**110.62 (103.24 – 118.53)**	**-**

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%.

A biowaiver was sought for the additional strengths of 5 mg and 10 mg.

Discussion and overall conclusion

Bioequivalence study and bioanalysis:
The study design is satisfactory, and the study results are confirmative. Moreover, the bioanalytical method has been adequately validated.
However, since the product is formulated as a racemic preparation of the S- and R-stereoisomers of oxazepam, the Applicant was asked to discuss the possible need of a stereoselective bioanalytical method, taking the conditions listed in the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) section 4.1.5 into account. Available data primarily reflects oxazepam distribution and metabolism in other species than humans and its relevance is therefore unclear, but it may be concluded that the BE guideline conditions 1 (different pharmaco-kinetics) and 2 (pronounced difference in pharmacodynamics) seem to be fulfilled. Whether the 3rd condition (AUC ratio modified by difference in rate of absorption) is fulfilled or not, remains unknown. However, it is the view of the RMS that it is most unlikely that a possible difference in absorption rate between the oxazepam enantiomers would significantly affect the therapeutic equivalence between the test product and the reference product, since:
- oxazepam bioavailability is high and tmax is relatively short (~2 hrs), indicating that both the extent and the rate of absorption are high for both enantiomers.
- only a minor difference in tmax between the test and reference products was noted in the BE study (test/reference ratio = 1.07), indicating no relevant difference in rate of absorption between the formulations.
Hence, re-performance of the bioequivalence study with the use of a chiral bioanalytical method, is not considered warranted.

Biowaiver:
In support of the linear kinetics of oxazepam, the applicant primarily refers to an article, which indicates linear kinetics over the dose range 20 - 300 mg. The RMS acknowledges the relevance of this article and the assumption that linearity could most reasonably be extrapolated to the lower dose range 5 - 15 mg. Furthermore, an absolute bioavailability of 92.8 % has been determined following a 15 mg oral dose of oxazepam. Since the bioavailability is this high after the 15 mg dose, a less than

dose-proportional increase of oxazepam AUC in the dose interval 5 – 15 mg is considered unlikely. Taken together, these references strongly suggest linear pharmacokinetics in the dose range 5 – 15 mg. Consequently, the 15 mg dose should be equally (or more) sensitive in detecting potential differences between formulations as the lower strengths, and the absence of studies with the lower strengths is acceptable from a pharmacokinetic point of view.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Delipam.

Safety specification
The MAH has submitted the version 0.1 RMP dated 2022-03-29 and proposed the following summary 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
The submitted Risk Management Plan, version 0.1 signed 2022-03-29 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 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 PL 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.

In conclusion, the user test is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Delipam, is found adequate. There are no objections to approval of Delipam, 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 benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Delipam, 5 mg, 10 mg, 15 mg, tablet was positively finalised on 2023-05-03.

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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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