LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Tapentadol Depot Liconsa
(tapentadol tartrate)

SE/H/2160/01-06/DC

This module reflects the scientific discussion for the approval of Tapentadol Depot Liconsa. The procedure was finalised on 2022-04-21. 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 Tapentadol Depot Liconsa, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg prolonged-release tablets.

The active substance is tapentadol tartrate. 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 Tapentadol Depot Liconsa, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg prolonged-release tablets are generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, Laboratorios Liconsa S.A, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS):

AT, CZ, DK, FR, IT, PL and SK.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Palexia® retard 25 mg prolonged-release tablet authorised in Germany since 2012 with Grünenthal GmbH as marketing authorisation holder.

The reference products used in the bioequivalence studies are Palexia® retard 25 mg and 250 mg prolonged-release tablets from Italy with Grünenthal Italia S.r.l.. as marketing authorisation holder, Palexia® retard 50 mg, 100 mg, 150 mg, and 200 mg prolonged-release tablets from Austria with Grünenthal GmbH, Austria, as marketing authorisation holder and Palexia® retard 250 mg prolonged-release tablet from Germany with Grünenthal GmbH, Germany, as marketing authorisation holder.

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

Pharmacodynamic, pharmacokinetic, and toxicological properties of active substance are well known. As active substance 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 the tapentadol-products are generic products, it will not lead to an increased exposure to the environment.

There are no objections to approval of Tapentadol Depot Liconsa from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted ten bioequivalence studies comparing Tapentadol Depot Liconsa with the originator Palexia®. Single-dose fasting studies have been performed with all applied dose strengths (25 mg, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg). Single-dose studies in the fed state as well as multiple-dose studies have been performed with the dose strengths 50 mg and 250 mg.

The study results of the ten bioequivalence studies are summarised below. For details of study design, results, and other information, see Non-clinical/Clinical D70 AR and Non-clinical/Clinical D120 AR:

*** Study 0090-20,** Single dose 25 mg fasted: For AUC_{0-t}, $AUC_{0-\infty}$, 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%.
*** Study 0089-20,** Single dose 50 mg fasted: For AUC_{0-t}, $AUC_{0-\infty}$, 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%.
*** Study 0086-20,** Single dose 50 mg fed: For AUC_{0-t}, $AUC_{0-\infty}$, 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%.
*** Study 20-VIN-0364,** Multiple dose 50 mg fasted: For $AUC_{0-t,ss}$, $C_{max,ss}$, and $C_{t,ss}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.
*** Study 20-VIN-0536,** Single dose 100 mg fasted: For AUC_{0-t}, $AUC_{0-\infty}$ 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%.
* **Study 20-VIN-0218**, Single-dose 150 mg fasted: For AUC_{0-t}, $AUC_{0-\infty}$ 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%.
* **Study 20-VIN-0220**, Single-dose 200 mg fasted: For AUC_{0-t}, $AUC_{0-\infty}$ 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%.
* **Study 0625-18,** (250 mg single-dose fasting): For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test product 1 and reference products fell within the conventional acceptance range of 80.00-125.00%.
*** Study 0626-18,** (250 mg single-dose fed): For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test product 1 and reference products fell within the conventional acceptance range of 80.00-125.00%.
* **Study 001B20,** Multiple dose 250 mg fasted: For $AUC_{0-t,ss}$, $C_{max,ss}$, and $C_{t,ss}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Two additional single-dose studies were included in module 5; studies 0394-19 and 0770-18 (single-dose studies with the 100 mg strength in the fasted and fed state). These two studies were not performed with final formulation and hence not assessed by the RMS.

Tapentadol Depot Liconsa is a single-unit prolonged-release formulation. All strengths have the same qualitative composition and are manufactured by the same manufacturing process. The strengths of 25 mg and 50 mg (Homologous group I) are directly proportional in composition. Similarly, the strengths of 200 mg and 250 mg (Homologous group IV) are directly proportional in composition. The composition of the two remaining strengths 100 mg and 150 mg falls within the composition extremes of the 25 mg, 50 mg and 200 mg, 250 mg strengths. In addition, the two highest and two lowest strengths represent the extremes with regards to tablet shape.

Table 1. Summary of clinical strategy. Studies performed and biowaivers

Strength	Proportional composition Group	Shape	Fasted study	Fed study	Multiple dose study
25 mg	Group 1	Round	YES	Biowaiver	Biowaiver
50 mg	Group 1	Round	YES	YES	YES
100 mg	Group 2	Oblong	YES	Bracketing	Bracketing
150 mg	Group 3	Oblong	YES	Bracketing	Bracketing
200 mg	Group 4	Oblong	YES	Biowaiver	Biowaiver
250 mg	Group 4	Oblong	YES	YES	YES

Discussion and overall conclusion

Tapentadol Depot Liconsa is a single-unit prolonged-release formulation for which bioequivalence studies after single- and multiple-dose administration are adequate. Studies comparing the food-effect of both formulations are also adequate.

The studies have been performed in healthy volunteers with naltrexone as concomitant medication which is acceptable.

According to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), a single dose study under fasting conditions is required for all strengths for a single unit formulation that can be taken with or without food, or a bracketing approach is possible if justified.
Single dose fasted studies have been submitted for all applied strengths, see Table 1.

Waiving of single dose fed studies and multiple dose studies with the strengths 25 mg and 200 mg is acceptable from a pharmacokinetic point of view. For quality aspects of biowaiver, see the quality assessment.

Waiving of single dose fed studies and multiple dose studies with the strengths 100 mg and 150 mg is also acceptable from a pharmacokinetic point of view. For quality aspects of biowaiver, see the quality assessment.

Based on the submitted bioequivalence studies, Tapentadol Depot Liconsa tablet is considered bioequivalent with Palexia® prolonged release tablet.

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 applicant 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 the three tapentadol-products included in this report.

Safety specification
The applicantMAH has submitted version 2.0 RMP dated 09 August 2021 and proposed the following summary safety concerns:

Table 2. List of important risks and missing information

Important identified risks	- drug abuse and drug dependence
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 Risk Management Plan, version 2.0, signed 09 August 2021, is considered acceptable.

The applicant 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 of the PlL was Spanish.

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 quality of the product Tapentadol Depot Liconsa is found adequate. There are no objections to approval of Tapentadol Depot Liconsa from a non-clinical and clinical point of view.

Bioequivalence between the test and reference products 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 Tapentadol Depot Liconsa 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg prolonged-release tablets was positively finalised on 21 April 2022.

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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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