LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lurobran
(lurasidone hydrochloride)

SE/H/2651/001–005/DC

This module reflects the scientific discussion for the approval of Lurobran. The procedure was finalised on 2025-03-31. 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 Lurobran, 18,5 mg, 37 mg, 74 mg, 111 mg, 148 mg, Film-coated tablet.

The active substance is lurasidone hydrochloride. 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 Lurobran 18,5 mg, 37 mg and 74 mg, Film-coated tablet, is a generic Art. 10(1) applications submitted according to Directive 2001/83/EC.

The application for Lurobran, 111 mg and 148 mg Film-coated tablet, is a hybrid Art. 10(3) application submitted according to Directive 2001/83/EC.

The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, ES and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Latuda, 37 mg, Film-coated tablet authorised in the Union since 2014, with Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A. as marketing authorisation holder.

The reference product used in the bioequivalence study is Latuda, 37 mg, Film-coated tablet from ES with Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A. as marketing authorisation holder.

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 lurasidone are well known. As lurasidone is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

The pharmacology, pharmacokinetics and toxicology aspects in the non-clinical overview is adequate.

The applicant has provided a commitment letter stating that an ERA following the decision tree as per 2024 CHMP GL is under preparation and that a complete ERA will be submitted within 2 years of post-approval for procedure SE/H/2651/001-005/DC.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Lurobran with the reference product Latuda.

Pharmacokinetic properties of the active substance
Absorption: Lurasidone reaches peak serum concentrations in approximately 1-3 hours.

In a food effect study, lurasidone mean C_{max} and AUC increased approximately by 2-3-times and 1.5-2-times, respectively, when administered with food compared to the levels observed under fasting conditions. Therefore, lurasidone should be administered with food.

Linearity: The pharmacokinetics of lurasidone is dose-proportional within a total daily dose range of 18.5 mg to 148 mg.

Elimination: Following administration of lurasidone, the elimination half-life was 20-40 hours.

Study C1B01424
Methods
This was a single-dose, two-way crossover study conducted in 68 healthy volunteers, comparing Lurasidone, 37 mg, film-coated tablets with Latuda, 37 mg, film-coated tablets under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of lurasidone were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 2021-12-04 and 2022-01-06.

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 lurasidone, n=64.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**334.146 ± 103.016**	**65.144 ± 22.017**	**3.5 (1.0-8.0)**
Reference	**328.091 ± 105.778**	**65.852 ± 23.112**	**3.0 (1.0-6.0)**
***Ratio (90 % CI)**	**102.28 (99.22-105.44)**	**99.27 (93.19-105.75)**	**-**
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72} 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 18.5, 74, 111 and 148 mg.

Discussion and overall conclusion

The 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) and Lurasidone film-coated tablets 18.5, 37 and 74 mg product-specific bioequivalence guidance (EMA/CHMP/39336/2023). The bioanalytical method was adequately validated.

Absence of studies with the additional strengths of 18.5, 74, 111 and 148 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) are fulfilled and since the pharmacokinetics of lurasidone is linear between 18.5 mg and 148 mg.

Based on the submitted bioequivalence study, Lurobran is considered bioequivalent with Latuda.

Pharmacodynamics

Lurasidone is a selective blocking agent of dopamine and monoamine effects. Lurasidone binds strongly to dopaminergic D2- and to serotonergic 5-HT2A and 5-HT7- receptors and also blocks α2c-adrenergic receptors and α2a-adrenergic receptors. Lurasidone also exhibits partial agonism at the 5HT-1A receptor. Lurasidone does not bind to histaminergic or muscarinic receptors.

Lurasidone doses ranging from 9 to 74 mg administered to healthy subjects produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, in the caudate, putamen and ventral striatum detected by positron emission tomography. Lurasidone belongs to the benzisothiazole class. Although the mechanism of action of lurasidone not fully understood, it is believed to affect both dopamine and serotonin receptors.

Lurasidone is a full antagonist at dopamine D2 and serotonin 5-HT2A and 5-HT7 receptors. It is a partial agonist at the serotonin 5-HT1A receptor. Lurasidone, when compared to other atypical antipsychotics, has the highest binding affinity for the 5-HT7 receptor. It is the blockage of D2 and 5-HT2A receptors that confers the property of atypical antipsychotics lurasidone. Antagonism at the 5-HT7 receptor and partial agonism at the 5-HT1A contributes to the antidepressant properties of lurasidone. Lurasidone has low activity on muscarinic M1, histamine H1, alpha-1, and 2A adrenergic receptors. This activity level minimizes the risk of orthostatic hypotension, sedation, weight gain, and cognitive blunting associated with other antipsychotic agents.

Clinical efficacy and safety
No efficacy and safety studies have been conducted.

Efficacy and data were obtained from the literature and the Applicant presented data from 7 scientific publications from 2012-2021. One of these studies was a randomized controlled clinical trial with adults, and one was a pooled post hoc analysis of double-blind placebo-controlled studies including adolescents (13-25 years). Five of the 7 studies were open-label and 2 of these included adolescents from 13 years as in the proposed indication.

According to the Applicant, the safety of lurasidone has been evaluated at doses of 18.5 -148 mg in clinical studies in patients with schizophrenia treated for up to 52 weeks and in the post-marketing setting. The most common adverse drug reactions (ADRs) (≥ 10%) were akathisia, nausea and insomnia.

Post marketing reports of clinically serious cases of skin and other hypersensitivity reactions have been reported in association with lurasidone treatment, including some reports of Stevens- Johnson syndrome.

Events of interest to the class
Extrapyramidal symptoms (EPS): In the adult short-term placebo-controlled studies, the incidence of reported events related to EPS, excluding akathisia and restlessness, was 13.5% for lurasidone-treated subjects versus 5.8% for placebo-treated subjects. The incidence of akathisia for lurasidone-treated subjects was 12.9% versus 3.0% for placebo-treated subjects. In the adolescent short-term placebo-controlled study, the incidence of reported events related to EPS, excluding akathisia, was 5.1% for lurasidone-treated subjects versus 1.8% for placebo- treated subjects. The incidence of akathisia for lurasidone-treated subjects was 8.9% versus 1.8% for placebo-treated subjects.

Dystonia: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, difficulty swallowing, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity, higher potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

Venous thromboembolism: Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs - Frequency unknown.

The applicant has presented recently published clinical trials and studies relevant for the efficacy and safety of lurasidone and its proposed indication and posology, which includes the hybrid application of 111 mg and 148 mg tablets.

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 Lurobran.

Part II Safety specification

Table SVIII.1 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Pregnant or lactating women

Safety specification is in line with the reference product, which is acceptable.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 03 October 2024 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 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 Lurobran, is found adequate. There are no objections to approval of the application 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

Post approval commitments

Description	Due date
Update ERA in line with 2024 CHMP ERA guideline	Within 2 years from EoP

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

N/A

VII. APPROVAL

The decentralised procedure for Lurobran, 8,5 mg, 37 mg, 74 mg, 111 mg, 148 mg, Film-coated tablet was positively finalised on 2025-03-31.

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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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