COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lurasidon Teva 18.5 mg, 37 mg and 74 mg, film-coated tablets (lurasidone hydrochloride)

NL/H/5772/001-003/DC

Date: 9 December 2025

This module reflects the scientific discussion for the approval of Lurasidon 18.5 mg, 37 mg and 74 mg, film-coated tablets. The procedure was finalised on 29 May 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lurasidon Teva 18.5 mg, 37 mg and 74 mg, film-coated tablets, from Teva B.V.

The product is indicated for the treatment of schizophrenia in adults and adolescent aged 13 years and over.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Latuda 18.5 mg, 37 mg and 74 mg, film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/14/913) since 21 March 2014.

The concerned member states (CMS) involved in this procedure were Croatia, Czechia, Italy, Poland, Slovenia and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Lurasidon Teva 18.5 mg, 37 mg and 74 mg are film-coated tablets. The three different strengths can be distinguished by size, debossing, shape and colour.

Lurasidon Teva 18.5 mg
White to off-white, round tablets, debossed with “LL” on one side and plain on the other side, with a diameter of 6.1 mm, containing as active substance 18.6 mg of lurasidone, as lurasidone hydrochloride.

Lurasidon Teva 37 mg
White to off-white, round tablets, debossed with “LI” on one side and plain on the other side, with a diameter 8.1 mm, containing as active substance 37.2 mg of lurasidone, as lurasidone hydrochloride.

Lurasidon Teva 74 mg
Pale green to green, oval tablets, debossed with “LH” on one side and plain on the other side, with dimensions of 12.1 mm x 7.1 mm, containing as active substance 74.5 mg lurasidone, as lurasidone hydrochloride.

The excipients are:
Tablet core – microcrystalline cellulose (E460), mannitol (E421), hypromellose 2910 (E464), croscarmellose sodium (E468) and magnesium stearate (E470b).
Tablet coating 18.5 mg and 37 mg – hypromellose 2910 (E464), titanium dioxide (E171) and macrogol 8000 (E1521).
Tablet coating 74 mg – hypromellose 2910 (E464), titanium dioxide (E171), macrogol 8000 (E1521), iron oxide yellow (E172) and indigo carmine aluminium lake (E132).

The three tablet strengths are dose proportional.

The film-coated tablets are packed in oriented polyamide/aluminium/polyvinyl chloride//aluminium (OPA/Al/PVC//Al) blisters.

II.2 Drug Substance

The drug substance is lurasidone hydrochloride, an established substance not described in the Pharmacopoeia. The drug substance is a white to off white powder and is slightly soluble in methanol and practically insoluble in water. Lurasidone hydrochloride shows no polymorphism and consists of six chiral centres.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
Manufacturer 1
The manufacturing process consists of four stages. Before that, an intermediate derivate is manufactured through a reaction. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail. Control of genotoxic impurities has been adequately justified.

Manufacturer 2
The manufacturing process consists of five stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

<u>Quality control of drug substance</u>
The active substance specification has been established in-house by the MAH. The specification contains tests for appearance, solubility, identification, loss on drying, sulphated ash, related substances, assay, enantiomer content, HCl content, chloride content, residual solvents and XRD. The specification is acceptable, although the MAH is requested to provide

one consolidated specification applicable to drug substance from both manufacturers. Batch analytical data demonstrating compliance with this specification have been provided for three batches of each manufacturer.

Stability of drug substance

Manufacturer 1

Stability data on the active substance have been provided for three production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

Manufacturer 2

Based on the additional stability data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The development of the product has been described, the choice of excipients is justified and their functions explained. The choice of packaging and manufacturing process are justified.
Dissolution method development has been adequately described and the discriminating power has been sufficiently demonstrated.

Manufacturing process

The manufacturing process consists of a wet granulation method involving sieving, dry mixing, granulation, drying, milling, lubrication, compression, coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three minimum production scale batches per strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients cellulose microcrystalline (101 and 102), mannitol, hypromellose 2910, croscarmellose sodium, magnesium stearate, titanium dioxide, macrogol 8000, iron oxide yellow and FD&C blue #2/indigo carmine aluminium lake comply with Ph. Eur. requirements. In addition, iron oxide yellow and FD&C blue #2/indigo carmine aluminium lake comply with the EU Regulation 231/2012. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average weight, disintegration, uniformity of dosage units (by content uniformity), identification, identification of colourants, water content, dissolution, assay, related substances and microbiological tests. Release and shelf-life requirements are identical, and is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An

adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scaled batches per strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from nine commercial scaled batches stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lurasidon Teva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH commits to submit a post-authorisation ASMF update from version 06 to the most recent version for manufacturer 2, by means of an appropriate variation application.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lurasidon Teva is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Latuda which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-

clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lurasidone is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Lurasidon Teva 37 mg, film-coated tablets (Teva B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Latuda 37 mg, film-coated tablets (Aziende Chimiche Riunite Angelini Francesco S.p.A., Italy).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements according to the EMA Bioequivalence guideline are met for the biowaiver for the 18.5 mg and 74 mg strengths:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%) in media with pH 1.2 and 4.5). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. At pH

6.8, the dissolution profiles showed a dissolution percentage below 2 at all-time points for all strengths and can thus be considered similar. This is acceptable.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 56 healthy male subjects, aged 19-44 years. Each subject received a single dose (37 mg) of one of the two lurasidone formulations. After an overnight fasting of at least ten hours, the subjects were served a standardised high-fat & high-calorie (926 calories) breakfast. The tablet was orally administered with 240 ml water 30 minutes after breakfast. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Lurasidone must be taken with reference to food intake. The film-coated tablets are to be taken once daily together with a meal. If taken without food, it is anticipated that lurasidone exposure will be significantly lower as compared to when taken with food.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Out of the 56 subjects, three subjects were withdrawn from the study due to protocol violations, one subject was withdrawn due to an adverse event (injury) and one subject did not report to the facility for the second period. The remaining 51 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lurasidone, 37 mg under fed conditions.

Treatment N=51	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	324.23 ± 122.02	72.94 ± 32.61	3.67 (1.00 – 5.00)
Reference	317.64 ± 129.09	69.20 ± 29.67	2.67 (1.00 – 5.00)
***Ratio (90% CI)**	1.04 (0.97 – 1.11)	1.05 (0.97 – 1.13)	-

AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Lurasidon Teva 37 mg is considered bioequivalent with Latuda 37 mg.

The results of the bioequivalence study with 37 mg formulation (study number C1B01243) can be extrapolated to other strengths 18.5 mg and 74 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Lurasidon Teva. At the time of approval, the most recent version of the RMP was version 1.1 dated 5 April 2024.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	Pregnant or lactating women

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Latuda. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Latuda 18.5 mg, 37 mg and 74 mg, film-coated tablets, EMEA/H/C/002713 for text and to Enoxy Depot 10 mg, 20 mg, 40 mg and 80 mg, prolonged-release tablets, SE/H/2082/001-004/DC for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lurasidon Teva 18.5 mg, 37 mg and 74 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Latuda 18.5 mg, 37 mg and 74 mg, film-coated tablets. Latuda is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lurasidon Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 May 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5772/001-3/II/001	Change in manufacture of the active substance - Other variation: Update of ASMF	No	27-04-2025	Approved	N.A.
NL/H/5772/001-3/IB/002	Change in the (invented) name of the medicinal product - for Nationally Authorised products	Yes	08-07-2025	Approved	N.A.