COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Raloxifeen HCl Aurobindo 60 mg, film-coated tablets (raloxifene hydrochloride)

NL/H/6437/001/DC

Date: 23 July 2025

This module reflects the scientific discussion for the approval of Raloxifeen HCl Aurobindo 60 mg, film-coated tablets. The procedure was finalised at 14 September 2016 in Portugal (PT/H/1515/001/DC). After a transfer on 27 may 2025, the current RMS is the Netherlands. For information on changes after the finalisation 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 agreed in granting a marketing authorisation for Raloxifeen HCl Aurobindo 60 mg, film-coated tablets, from Aurobindo Pharma B.V.

Raloxifeen HCl Aurobindo is indicated for the treatment and prevention of osteoporosis in postmenopausal women. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.

When determining the choice of Raloxifene Aurovitas or other therapies, including oestrogens, for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on uterine and breast tissues, and cardiovascular risks and benefits
A comprehensive description of the indications and posology is given in the SmPC."

This decentralised procedure application concerns a generic version of Raloxifene, 60 mg film-coated tablets under the trade name Raloxifeen HCl Aurobindo

The originator product is Evista (60 mg, film-coated tablets) by Daiichi Sankyo Europe GmbH, registered in the European Union since 05.08.1998.

The marketing authorization was granted on 20-04-2017 based on Directive 2001/83/EC article 10.1 (a) (iii) first paragraph and the Marketing Authorisation Holder is Aurobindo Pharma B.V.

With Portugal as the Reference Member State (RMS) in this Decentralized Procedure Aurobindo Pharma B.V. is applying for the Marketing Authorisations for Raloxifeen HCl Aurobindo in ES and NL (CMS).

II. QUALITY ASPECTS

II.1 Introduction

Film-coated tablet

White to off-white, elliptical, film-coated tablets debossed with 'X' on one side and '57' on the other side.

The other excipients are

Tablet core: Cellulose microcrystalline, crospovidone (Type-A), povidone (K - 30), polysorbate 80, Citric acid monohydrate, magnesium stearate.

Tablet coating: Hypromellose, titanium dioxide (E171), macrogol 400, polysorbate 80.

Raloxifeen HCl Aurobindo film-coated tablets are available in Polyamide/Aluminium/PVC/Aluminium foil blister pack contains 14, 28, 30, 50, 56 and 90 film-coated tablets.

II.2 Drug Substance

Nomenclature

INN: Raloxifene Hydrochloride

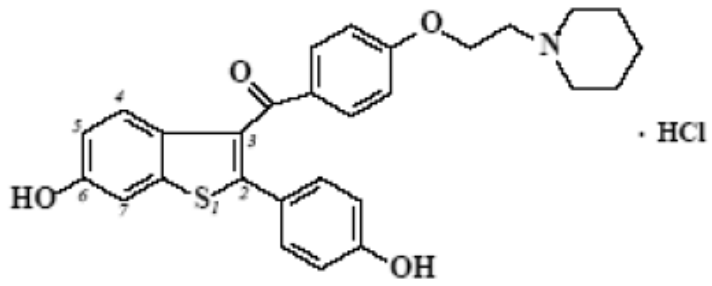
Generic name: Raloxifene Hydrochloride

Chemical names: 6-hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl][4- [2-(piperidin-1-yl)ethoxy]phenyl]methanone hydrochloride

Or

6-hydroxy-2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl) ethoxy]benzoyl]benzo[b]-thiophene hydrochloride

Structure (structural formula)



Molecular formula: C28H27NO4S.HCl

Relative molecular mass: 510

Stereochemistry	Raloxifene molecule does not have any asymmetric carbon atom and hence there is no possibility of optical isomerism
Polymorphism	Several Solvates of Raloxifene hydrochloride with solvents such as, methylene chloride, 1,2- dichloroethane, chloroform, 1,2,3-trichloropropane and aromatic solvents etc. are known in Chemical literature.

General properties (physico-chemical characterisation)

Description	Almost white or pale yellow powder
Solubility	Very slightly soluble or practically insoluble in water and in acetone

Manufacturing process

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Raloxifeen HCl Aurobindo are of sufficient quality in view of the present European regulatory requirements.

Quality control of drug substance

The control tests and specifications for drug substance product are adequately drawn up.

Stability of drug substance

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained.

Quality control of drug product

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
The proposed shelf-life of 36 months for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of Raloxifene are well known. As Raloxifene is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Raloxifeen HCl Aurobindo 60 mg, film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 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 Introduction

Raloxifeen HCl Aurobindo film-coated tablets were developed in line with the originator product commercially available, Evista® 60mg film coated tablets by Daiichi Sankyo Europe GmbH, Munich, Germany, marketed in the European Union.

IV.2 Pharmacokinetics

A bioequivalence study was performed, in order to demonstrate bioequivalence between the developed Raloxifeen HCl Aurobindo 60 mg, film-coated tablets, and the originator product, Evista®. The formulation used in the bioequivalence study was the same as the to-be-marketed formulation, which is presented within this marketing authorisation application.

Bioequivalence studies

An open label, randomized, two-treatment, two-sequence, four-period, replicate, cross-over, single-dose comparative oral bioavailability study of Raloxifene Hydrochloride tablets 60 mg (Test) of Aurobindo Pharma Limited., India and Evista 60 mg tablets (Reference) of Daiichi Sankyo Europe GmbH, Germany in 48 healthy, adult, human subjects under fasting conditions.

Raloxifeen HCl Aurobindo film-coated tablets is formulated in only one strength (60 mg) and no biowaiver is required.

Conclusion on bioequivalence studies

Based on the submitted bioequivalence study Raloxifeen HCl Aurobindo 60 mg, film-coated

tablets is considered bioequivalent with Evista 60 mg, film-coated tablets.

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 Raloxifeen HCl Aurobindo 60 mg, film-coated tablets.

TABLE 2. SUMMARY OF SAFETY CONCERNS

Important Identified Risks	Risk of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis, superficial vein thrombophlebitis
	Use in patients with hepatic impairment including cholestasis
	Use in patients with severe renal impairment.
	Risk of fatal stroke
	Unexplained Uterine bleeding
	Foetal harm/teratogenicity
	Hypertriglyceridemia
	Flu syndrome
	Vasodilatation (hot flushes)
Important Potential Risks	Use in patients with endometrial cancer
	Drug interactions with estrogens
	Drug interactions with warfarin
Missing Information	Usein patients with breast cancer
	Use during lactation

IV.4 Discussion on the clinical aspects

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorized medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. This generic product can be used instead of its reference product.

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.
The proposed PIL text is in line with the Centrally approved reference medicinal product (EVISTA) text as approved by EMEA (Ref.No: EMEA/H/C/000184) and date of issuing marketing authorization valid throughout the European Union is 05.08.1998.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Raloxifeen HCl Aurobindo 60 mg, film-coated tablets contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

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
PT/H/1515/1/IA/001	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - Updated certificate from an already approved manufacturer	No	19 February 2019	Approved	N.A.
PT/H/1515/1/R/001	Renewal	No	25 April 2022	Approved	N.A.
PT/H/1515/1/IA/002	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - Updated certificate from an already approved manufacturer	No	18 March 2021	Approved	N.A.
PT/H/1515/1/IA/003/G	Deletion of manufacturing sites (including for an active substance, intermediate or	Yes	22 April 2021	Approved	N.A.

	finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)).				
PT/H/1515/1/IA/004	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance Minor changes to an approved test procedure	No	19 July 2024	Approved	N.A.
PT/H/1515/1/IA/005	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - Updated certificate from an already approved manufacturer	No	9 June 2024	Approved	N.A.