COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Acebutolol Aurobindo 200 mg and 400 mg, film-coated tablets

(acebutolol hydrochloride)

NL/H/4727/001-002/DC

Date: 31 October 2022

This module reflects the scientific discussion for the approval of Acebutolol Aurobindo 200 mg and 400 mg, film-coated tablets. The procedure was finalised at 10 January 2018 in Portugal (PT/H/1796/001-002). After a transfer on 11 April 2019, the current RMS is the Netherlands. 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
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
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 Acebutolol Aurobindo 200 mg and 400 mg, film-coated tablets, from marketing authorisation holder (MAH) Aurobindo Pharma B.V.

The product is indicated for the management of hypertension, angina pectoris and the control of tachyarrhythmias.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sectral which has been available for clinical use and marketed for more than 10 years in most countries worldwide.

For the different strengths, different concerned member states (CMS) were involved in the procedure:
200 mg strength – Poland and The Netherlands*;*
400 mg strength – Czech Republic, Poland, The Netherlands and United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Acebutolol 200mg film-coated tablets:
White to off-white, round shaped biconvex film coated tablets of 10.1 mm debossed with 'AC' and '2' separated with break line on one side and plain on the other side.

Acebutolol 400mg film-coated tablets:
White to off-white, oblong shaped biconvex film coated tablets having the length approximately 17.15 mm, diameter of body approximately 8.42 mm debossed with 'AC' and '4' separated with break line on one side and plain on the other side.

The tablet can be divided into equal doses.

The active substance is acebutolol hydrochloride. Each film-coated tablet contains 200 mg or 400 mg of acebutolol (as acebutolol hydrochloride)

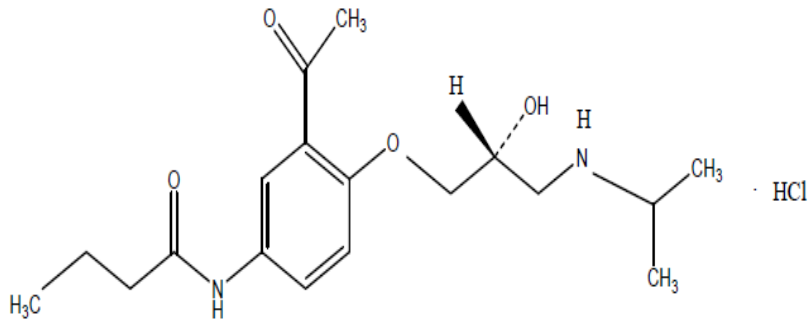
The excipients are:
Tablet core: lactose monohydrate, maize starch, povidone (K-30), talc, silica colloidal anhydrous, magnesium stearate
Tablet coat: hypromellose 6cp, macrogol 6000, titanium dioxide (E171)

Acebutolol Aurobindo tablets are available in Clear PVC– Aluminium foil blister packs.

II.2 Drug Substance

Nomenclature
INN: acebutolol hydrochloride
Generic name: acebutolol hydrochloride
Chemical names: N-[3-Acetyl-4-[(2RS)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl] butanamide hydrochloride
CAS Reg. No.: [34381-68-5]

Structure (structural formula)



Molecular formula: C18H28N2O4. HCl
Relative molecular mass: 372.9
Polymorphism: Acebutolol hydrochloride does not exhibit polymorphism.
Isomerism: Acebutolol hydrochloride has one chiral centre. It exists as racemic compound

General properties (physic-chemical characterisation)
A white or almost white, crystalline powder that is freely soluble in water and in ethanol (96 %), very slightly soluble in acetone and in methylene chloride.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The chemical-pharmaceutical documentation and quality overall summary in relation to Acebutolol Aurobindo are of sufficient quality in view of the present European regulatory requirements. 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. The proposed retest period of 60 months is justified in the CEP.

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 two batches of each strength. The batch analysis results show that the finished products meet the proposed specifications.

Stability of the 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 24 months with storage below 30ºC for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Acebutolol Aurobindo 200 mg and 400 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

Pharmacodynamic, pharmacokinetic and toxicological properties of acebutolol are well known. As acebutolol 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.

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

To support the application, the MAH has submitted one bioequivalence study under fasting conditions conducted with the 400 mg strength.

IV.2 Pharmacokinetics

Based on the EMA - Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), a single-dose comparative bioavailability study is adequate to demonstrate bioequivalence between test and reference formulations for oral administration (immediate-release formulations with systemic action). Bioequivalence was tested under fasting conditions with the higher strength (400 mg). In principle, the submitted bioequivalence study is considered adequate and sufficient to support registration.

Protocol code:	RP.16.0431
Title of the study:	"*An open label, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose comparative oral bioequivalence study of Acebutolol Tablets BP 400 mg (Test) of Aurobindo Pharma Limited., India and SECTRAL® 400 mg Tablets (Reference) of SANOFI-AVENTIS, France, in 36 healthy, adult, human subjects under fasting conditions*."

<u>Biowaiver</u>
A biowaiver is requested for Acebutolol 200 mg Tablets as per following considerations:
[Ref.: CPMP Guideline on Investigation of Bioequivalence].

1. The pharmaceutical products are manufactured by the same manufacturing process.
2. The drug input has been shown to be linear over the therapeutic dose range. If this is not the case the strengths where the sensitivity is largest to identify the differences in the two products should be used.
3. The qualitative composition of the different strengths is the same.

4. The composition of the strengths are quantitatively proportional i.e. the ratio between active substance and the excipients is the same.
5. The dissolution profile should be similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study.

All conditions for the biowaiver requested for the additional strength (Acebutolol 200 mg film-coated tablets) are fulfilled.

Conclusion on bioequivalence study

Based on the submitted bioequivalence study Acebutolol Aurobindo 200 and 400 mg film coated tablets is considered bioequivalent with Sectral 200 mg and 400 mg Film coated tablet.

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 Acebutolol Aurobindo 200 mg and 400 mg, film-coated tablets.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Decompensation of heart failure • Bradycardia • Hypotension • Bronchospasm • Second or third degree AV block • Cardiogenic shock • Decreased diabetic control and masking of hypoglycaemic effects • Hypersensitivity, including anaphylactic reactions • Severe exacerbation of angina and precipitation of ischaemic heart disease due to abrupt discontinuation of acebutolol
Important potential risks	• Pneumonitis • Peronei's disease • Exacerbation of psoriasis • Lupus like syndrome • Peripheral circulatory disorders • Prinzmetal's angina • Chronic obstructive pulmonary disease (COPD) • Use in pregnancy and lactation
Missing information	• Use in paediatric population

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

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' authorised 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 reference medicinal product Sectral, which has been authorised in EU through National procedure. Furthermore Aurobindo Pharma Limited has performed user testing on the PIL of Metoprolol Aurobindo 50 and 100 mg film-coated tablets (Parent PIL), which was already assessed and approved during the DCP no.: (SE/HII20IIOOI-002/DC).

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Acebutolol Aurobindo 200 mg and 400 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.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Acebutolol Aurobindo 200 mg and 400 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10-01-2018.

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/4727/1-2/IA/001	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	No	02-01-2020	Approved	N/A
NL/H/4727/1-2/IB/002	Extension of the shelf life of the finished product	Yes	06-08-2020	Approved	N/A
NL/H/4727/1-2/IA/003	Change in the batch size (including batch size ranges) of the finished product Up to 10-fold compared to the originally approved batch size	No	07-12-2020	Approved	N/A
NL/H/4727/1-2/IA/004	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance New certificate from a new manufacturer (replacement or addition)	No	08-06-2021	Approved	N/A
NL/H/4727/1-2/IA/006	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance Deletion of certificates (in case multiple certificates exist per material)	No	09-08-2022	Approved	N/A