LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metoprolol Aurobindo
(metoprolol tartrate)

SE/H/1201/01-02/DC

This module reflects the scientific discussion for the approval of Metoprolol Aurobindo. The procedure was finalised at 2012-11-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Aurobindo Pharma Limited has applied for a marketing authorisation for Metoprolol Aurobindo, 50 mg and 100 mg, film-coated tablets, claiming essential similarity to Seloken, 50 mg and 100 mg, tablet, marketed in Sweden by AstraZeneca AB. The product contains metoprolol tartrate as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Seloken, 100 mg, tablets, marketed by Astra Zeneca S.p.A in Italy.

II. QUALITY ASPECTS

II.1 Introduction

Metoprolol Aurobindo is presented in the form of film coated tablets containing 50 respective 100 mg of metoprolol tartrate. The excipients are cellulose microcrystalline, maize starch, sodium starch glycolate (Type A), silica colloidal anhydrous, maize starch, sodium laurilsulphate, talc, magnesium stearate and purified water. The tablets are film coated and the coating includes hypromellose, titanium dioxide, macrogol (only 100 mg tablet), talc, polysorbate 80, iron oxide red (only 50 mg tablet), indigo carmine aluminium lake (only 100 mg tablet) and purified water. The tablets are packed in clear PVC/PVDC-aluminium foil blister and in HDPE bottles.

II.2 Drug Substance

Metoprolol tartrate has a monograph in the Ph Eur.

Metoprolol tartrate is a white, crystalline powder or colourless crystals which is very soluble in water and slightly soluble in alcohol. The structure of Metoprolol tartrate has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Metoprolol Aurobindo, film coated tablet is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 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 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Metoprolol Aurobindo, 100 mg, tablet with Seloken, 100 mg, tablet under fasting conditions. The study was conducted at AXIS Clinicals Limited, Miyapur, Hyderabad, India between 11/04/12 and 20/04/12. Blood samples were collected pre-dose and up to 24 hours post-dose. The study design is considered acceptable. Plasma concentrations of metoprolol were determined with an adequately validated LC/MS/MS method. For AUC_{0-t} 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%; bioequivalence was demonstrated.

IV.2 Discussion on the 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 clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 the PIL was English.
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.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Metoprolol Aurobindo, 50 mg and 100 mg, film-coated tablets, is recommended for approval

VI. APPROVAL

The Decentralised procedure for Metoprolol Aurobindo, 50 mg and 100 mg, film-coated tablets, was successfully finalised on 2012-11-22.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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