

Public Assessment Report

Scientific discussion

Metoprolol ratiopharm (metoprolol succinate)

SE/H/0760/001-004/DC

This module reflects the scientific discussion for the approval of Metoprolol ratiopharm. The procedure was finalised at 2009-01-30. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

ratiopharm GmbH has applied for a marketing authorisation for Metoprolol ratiopharm, prolonged-release tablets, 25, 50, 100 and 200 mg claiming essential similarity to Seloken ZOC prolonged-release tablets, 25, 50, 100 and 200 mg marketed in Sweden by AstraZeneca. The product contains metoprolol succinate as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Beloc-Zok forte marketed by AstraZeneca GmbH in Germany.

II. QUALITY ASPECTS

II.1 Introduction

Metoprolol ratiopharm is presented in the form of prolonged release tablets containing metoprolol succinate corresponding to 25, 50, 100 and 200 mg of metoprolol tartrate. The excipients are sugar spheres (containing sucrose and maize starch), macrogol, ethyl acrylate-methyl methacrylate copolymer, talc, povidone, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, hypromellose and titanium dioxide. The tablets are packed in Al/Al blisters or HDPE bottles.

II.2 Drug Substance

Metoprolol succinate has a monograph in the Ph Eur.

Metoprolol succinate is a white, crystalline powder which is freely soluble in water. The structure of metoprolol succinate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. 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 ratiopharm prolonged-release tablets are 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, when stored below 25°C.

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

The applications was supported by three clinical studies to demonstrate the bioequivalence between the generic product and the originator, each study testing the highest tablet strength (190 mg metoprolol succinate) in healthy subjects. The studies were two single-dose studies in fasted and fed state, respectively, and a repeat-dose study in fasted state. All studies were open-label, balanced, and randomised, two-treatment, two-period, two-sequence, crossover, comparative oral bioavailability studies. In each period of the fasted single-dose study, subjects were administered 190 mg metoprolol succinate in the morning after an overnight fast and continued to fast for 4 hours post-dose. In the fed study, the tablet was administered within 30 minutes after the subjects had been served a high-fat, high-calorie breakfast. Blood sampling was performed for 48 hours post-dose. In the multiple-dose study, in each period metoprolol 190 mg tablets were administered once daily for 6 days in the fasted state. Predose blood samples were collected on all dosing days and post-dose samples for 24 hours after dose 6. The concentrations of metoprolol in plasma were analysed by an LC-MS/MS method.

Bioequivalence was to be based on C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ in the single-dose studies and C_{max-ss} , C_{min-ss} , and AUC_{τ} , in the multiple-dose study. The acceptance criteria for bioequivalence of AUC values were defined as confidence intervals (CIs) for the test/reference ratio within 80.00% to 125.00%. For C_{max} and, in the multiple-dose study, C_{min} , the acceptance criteria were defined as CIs for the test/reference ratio within 75.00% to 133.00%.

The study package and the primary pharmacokinetic parameters for evaluation were appropriate for studying bioequivalence between two metoprolol prolonged-release formulations. The widening of the acceptance range for C_{min} was acceptable since the Applicant demonstrated that the intra-individual, day-to-day variability in C_{min} for the reference formulation was >30% at steady state in the multiple-dose bioequivalence study. As the 90% CIs for C_{max} fell within the normal acceptance range in all three studies (see below), widening of the acceptance range for C_{max} was not an issue for this application.

The pharmacokinetic results of the three bioequivalence studies are shown in Tables 1-3.

Table 1. Pharmacokinetic parameters of metoprolol after administration of a **single dose** of 190 mg metoprolol in the **fasted state** (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ as median, range)

Treatment	AUC _{0-t} ng*h/ml	AUC _{0-∞} ng*h/ml	C _{max} ng/ml	t _{max} h	T _{1/2} h
Test	1602 $\pm$ 980	1624 $\pm$ 1000	91.4 $\pm$ 44.9	10.0	5.01 $\pm$ 0.98
Reference	1700 $\pm$ 983	1718 $\pm$ 1003	88.0 $\pm$ 39.7	10.0	5.25 $\pm$ 0.86
*Ratio (%)	93.0	93.5	101.9	-	-
90% CI	85.63 – 100.98	86.23 – 101.40	97.32 – 106.67	-	-
AUC _{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration T _{max} time for maximum concentration T _{1/2} half-life					

*ln-transformed values

Table 2. Pharmacokinetic parameters of metoprolol after administration of a **single dose** of 190 mg metoprolol in the **fed state** (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ as median, range)

Treatment	AUC _{0-t} ng*h/ml	AUC _{0-∞} ng*h/ml	C _{max} ng/ml	t _{max} h	T _{1/2} h
Test	2365 $\pm$ 1528	2410 $\pm$ 1596	118.4 $\pm$ 56.9	11.0	5.45 $\pm$ 1.23
Reference	2259 $\pm$ 1436	2300 $\pm$ 1508	113.6 $\pm$ 54.5	10.0	5.47 $\pm$ 1.3
*Ratio (%)	102.9	103.1	105.0	-	-
90% CI	96.47 - 109.75	96.66 - 109.88	98.22 – 112.21	-	-
AUC _{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration T _{max} time for maximum concentration T _{1/2} half-life					

*ln-transformed values

Table 3. Pharmacokinetic parameters of metoprolol at **steady-state** (day 6) after dosing with 190 mg metoprolol daily for 6 days in the fasted state (non-transformed values; arithmetic mean $\pm$ SD, T_{max} median)

Treatment	AUC _{0-τ} ng*hr/ml	C _{max, ss} ng/ml	C _{min, ss} ^{a)} ng/ml	T _{max} (hr)	PTF% %
Test	3167 $\pm$ 2208	180.1 $\pm$ 112.5	79.2 $\pm$ 70.2	132.0	94.3 $\pm$ 45.0
Reference	3006 $\pm$ 1927	170.3 $\pm$ 95.1	74.1 $\pm$ 66.2	129.0	97.9 $\pm$ 50.8
Ratio (%)	102.6	102.7	110.6	-	-
90% CI	94.92 – 110.95	96.31 – 109.54	93.39 – 130.92	-	-
AUC _{0-τ} area under the plasma concentration-time curve during the 24-hr dose interval C _{max} maximum plasma concentration C _{min} minimum plasma concentration (24-hr concentration) T _{max} refers to the whole dosing period (day 1-6) with dose 6 given at 120 hr PTF% fluctuation index					

a) C_{min-ss} is the concentration in the 24-hr sample after dose 6

Bioequivalence between the test and reference formulation was demonstrated for $C_{\max}$ and AUC within the normal acceptance criteria of 80.00-125.00% in all three studies. Bioequivalence between the test and reference formulation was demonstrated for $C_{\min}$ in the multiple-dose study using the wider acceptance criteria of 75.00-133.00%.

The Applicant also provided bioequivalence analysis of the peak-to-trough fluctuation (PTF) in the multiple-dose study, demonstrating that the test and reference formulations are bioequivalent (within the 80-125% limits) in this respect.

Thus, the generic product was concluded to be bioequivalent with the originator.

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 testing of the package leaflet has been performed and is acceptable.

The results of the conducted bioequivalence studies 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 ratiopharm, prolonged-release tablets, 25, 50, 100 and 200 mg is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Metoprolol ratiopharm, prolonged-release tablets, 25, 50, 100 and 200 mg was successfully finalised on 2009-01-30.

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)