Public Assessment Report

Scientific discussion

Metoprololsuccinat "Actavis"

Prolonged release tablets
25 mg, 50 mg, 100 mg and 200 mg

Metoprolol succinate

This module reflects the scientific discussion for the approval of Metoprolosuccinat "Actavis". The procedure was finalised on 13 August 2008. For information on changes after this date please refer to the module 'Update'.

I.   INTRODUCTION

This assessment report concerns a generic version of metoprolol succinate prolonged release tablets 25 mg, 50 mg, 100 mg and 200 mg approved through DCP on 13 August 2008 under the trade name of Metoprololsuccinat "Actavis" name with Denmark acting as RMS.

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS and CMS have approved the application for Metoprololsuccinat "Actavis" prolonged release tablets 25 mg, 50 mg, 100 mg and 200 mg indicated for the treatment of:

- Hypertension,
- Angina pectoris,
- Heart arrhythmia, particularly supraventricular tachycardia,
- Prophylaxis to prevent heart death and reinfarction after the acute phase of myocardial infarction,
- Palpitations in the absence of organic heart diseases,
- Prophylaxis against migraine,
- Stabile, symptom-producing heart failure (NYHA II-IV, left ventricular ejection fraction < 40 %), combined with other heart failure therapies.

The application is submitted according to Article 10(1) 'generic application' of Directive 2001/83/EEC as amended.

The originator product is Selo-zok 23.75, 47.5, 95 and 190 mg metoprolol succinate (corresponding to 25, 50, 100 and 200 mg metoprolol tartrate) prolonged release tablets by AstraZeneca, registered since 1986 (50, 100 and 200 mg) and 2000 (25 mg).
In Denmark the Brand Leader is Selo-zok prolonged release tablets by AstraZeneca.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II.   QUALITY ASPECTS

II.1   Introduction

The chemical-pharmaceutical documentation and Expert Report in relation to metoprolol succinate prolonged release tablets are of sufficient quality in view of the present European regulatory requirements.

The finished product is presented as prolonged release film-coated tablets in the strength of 23.75, 47.5, 95 and 190 mg metoprolol succinate (corresponding to 25, 50, 100 and 200 mg metoprolol tartrate) packed in blisters (PVC-PE-PVDC/Al) available in packs containing 10, 14, 20, 28, 30, 50, 50x1, 56, 60, 98 and 100 prolonged-release tablets. The tablets are white, oval biconvex and scored on both sides.

The tablet core consists of: Cellulose, microcrystalline; Methylcellulose; Maize starch; Glycerol; Ethylcellulose and Magnesium stearate.

The tablet coating consists of: Hypromellose; Cellulose, microcrystalline; Macrogol stearate and Titanium dioxide (E171).

II.2 Drug Substance

The documentation on the drug substance is presented as a CEP.

The drug substance is controlled according to requirements of Ph. Eur. supplemented with limit on isopropyl amine (cf. CEP) and particle size distribution.

Stability studies constitute the basis for the agreed re-test period.

II.3 Medicinal Product

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

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/three pilot scale batches of each strength. The batch analysis results show that the finished products meet the specifications proposed.

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 (do not store above 30°C) for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Specific non-clinical studies have not been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended.

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

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The report refers 49 publications up to year 2005.

IV. CLINICAL ASPECTS

IV.1 Introduction

No specific clinical studies, apart from the bioequivalence studies, have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended.

The clinical overview presents a satisfactory overview of clinical pharmacology, efficacy and safety. The clinical overview is adequate. The report refers 68 publications up to year 2005.

An addendum to the clinical overview has been presented. The addendum has been written due to the performance of an additional multiple-dose bioequivalence study with the formulation intended for marketing.

To support the application, the Applicant has submitted as report 6 bioequivalence studies.

IV.2   Pharmacokinetics

General description

Metoprolol succinate is completely absorbed after oral administration. Owing to an extensive first pass effect, the systemic bioavailability of metoprolol from a single oral dose is approximately 50%. The bioavailability is reduced by about 20-30% for the controlled release formulation compared with conventional tablets. However, this is not of significance for clinical efficacy, since the area under the effect curve for heart rate is the same as for conventional tablets.
The pharmacokinetics of metoprolol are linear over the dosage range.

The plasma protein binding of metoprolol is low, approximately 5-10%. The controlled release tablet is formulated to release metoprolol continuously for about 20 hours. In contrast to immediate release formulations, ingestion of metoprolol prolonged release formulation with food only leads to a small increase in systemic bioavailability (mean 5% vs. 40% for immediate release formulation) compared to the fasting state.

Metoprolol undergoes oxidative metabolism in the liver primarily by CYP2D6. Three main metabolites have been identified; however, none of them have a beta-blocking effect of clinical importance. In general 95% of an oral dose can be recovered in the urine. About 5% of a given dose is excreted in the urine in unchanged form; this can in some cases be up to 30%. The elimination half-life of metoprolol in plasma is in average 3.5 hours (range: 1-9 hours).

Bioequivalence

In the submitted dossier four bioequivalence studies were included in order to show essentially similarity of metoprolol succinate prolonged release tablet with the brand-leader Selo-zok/Beloc-zok prolonged release tablets, AstraZeneca. The first 3 studies (single dose studies under fasting and fed conditions and multiple-dose study) were carried out with the initial developed formulation, which were further optimised to the formulation intended for marketing.
Since the multiple-dose study with the initial formulation did not comply with the established bioequivalence criteria with respect to C_{min}, a supportive multiple dose study was carried out with a batch of the optimised formulation.

All BE-studies were carried out with the 190 mg dosage strength. Sufficient justification for biowaivers for the three lower strengths has been given.

Bioequivalence was demonstrated for the initially developed metoprolol succinate prolonged release tablet after single-dose administration in fasting and fed conditions. However, after multiple-dose administration bioequivalence was shown for the optimised formulation but not for the initial formulation regarding C_{min}, which were outside the lower limit of the acceptance range of 80-125%. Therefore, it is not evident that a difference in bioavailability for the initial and optimised formulations are not present and hence omission of single-dose bioequivalence studies with the optimised formulation intended for marketing was not considered justified.
In the Day 106 response, study reports were presented for 2 additional single-dose studies carried out under fasting and fed conditions, respectively, with the final formulation intended for marketing.
Bioequivalence between the test and reference product was demonstrated after single-dose administration, since the 90% confidence interval for all primary variables AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} was within 80-125% under both fasting and fed conditions.

BE study 1 - Single dose, fasting conditions

Study design
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 190 mg was administered in each period.

The subjects were fasting overnight for at least 10 hours before drug administration and for at least 4 hours thereafter. Water was allowed *ad libitum* until 2 hours pre-dose and from 2 hours after drug administration. Standardised meals were served at appropriate times during the study.
The subjects were housed at the clinic until the 36-hours blood-draw and returned to the clinic for the last 48-hour blood-draw.

Blood samples were collected pre-dosing and at time points up to 48.0 hours post administration of a single-dose 190 mg prolonged release tablet with 240 ml of water for the analyses of metoprolol.

Test and reference products
Metoprolol succinate 190 mg prolonged release tablets have been compared to Beloc-Zok forte 190 mg prolonged release tablets by AstraZeneca from the German market. The batch of the test product is the initially developed formulation before optimisation.

Satisfactory certificates of analysis of the test and reference product are presented.

Population(s) studied
39 healthy male and female subjects were enrolled in the study, but only 37 subjects were dosed since subject no. 17 and 31 had out of range vital signs before dosing of period 1. Of the 37 subjects (17 male and 20 female) participating in the study 36 were Caucasians and 1 Negroid, age: 19-44 years. 32 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Analytical methods
The samples were received frozen at the analytical facility and stored at -20±10°C until analysis.
The blood samples were analyzed by HPLC/MS/MS method for detection of metoprolol.
The analytical method has been validated.

Pharmacokinetic Variables
Method of assessment of pharmacokinetic parameters: Statistical and pharmacokinetic analyses were generated using Kinetic, version 4.1.1 and SAS version 9.1 (Mixed procedure).

Choice of primary variables and secondary PK variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{t/\infty}$, C_{max}, t_{max}, K_{el} and $t_{\frac{1}{2}\,el}$.
Primary variables: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Statistical methods
ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
The ANOVA model included sequence, subject nested within sequence, period and treatment.
Nonparametric test was carried out on t_{max}.

Criteria for conclusion of bioequivalence:
The 90% confidence interval for the exponential of the difference between the test and reference product for the ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ should be within 80-125%.

Results

Pharmacokinetic Parameters

Metoprolol (n=32)

PARAMETER	TEST		REFERENCE	
	MEAN	C.V.	MEAN	C.V.
C_{max} (ng/mL)	78.61	79.7	77.66	80.4
$\ln (C_{max})$ (ng/mL)	4.1076	18.3	4.0834	18.7
T_{max} (hours) *	5.50	40.7	12.00	36.0
AUC_T (ng·h/mL)	1864.78	108.8	1930.75	96.1
$\ln (AUC_T)$ (ng·h/mL)	7.1286	12.8	7.2159	12.0
AUC_∞ (ng·h/mL)	2011.43	117.3	2018.10	100.7
$\ln (AUC_\infty)$ (ng·h/mL)	7.1863	12.6	7.2554	11.7
$AUC_{T/\infty}$ (%)	94.53	5.2	96.26	5.1
K_{el} (hour^{-1})	0.0858	31.8	0.1031	22.7
$T\frac{1}{2}_{el}$ (hours)	8.98	34.1	7.10	25.6

* median is presented

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	60.13	58.87	102.13	95.60	109.11
AUC_T	1231.59	1347.97	91.37	87.40	95.51
AUC_∞	1304.76	1403.02	93.00	88.89	97.29

The 90% confidence interval for the ln-transformed primary variables C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ is within the acceptance range of 80-125%.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study the initially developed metoprolol succinate prolonged release tablets are considered bioequivalent with Beloc-Zok/Selo-Zok forte prolonged release tablets, AstraZeneca after single-dose administration in fasting conditions.

BE study 2 - Single dose, fed conditions

Study design
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fed conditions with a wash out period of 7 days between the two administrations. 190 mg was administered in each period.

After an overnight fast for at least 10 hours the subjects received a standardised high-fat, high calorie meal 30 minutes before drug administration. Water was allowed *ad libitum* until 2 hours pre-dose and from 2 hours after drug administration. A standardised meal was served at least 4 hours after drug administration and at appropriate times thereafter during the study.
The subjects were housed at the clinic until the 36-hours blood-draw and returned to the clinic for the last 48-hour blood-draw.

Blood samples were collected pre-dosing and at time points up to 48.0 hours post administration of a single-dose 190 mg prolonged release tablet with 240 ml of water for the analyses of metoprolol.

Test and reference products

Metoprolol succinate 190 mg prolonged release tablets have been compared to Beloc-Zok forte 190 mg prolonged release tablets by AstraZeneca from the German market. The batch of the test product is the initially developed formulation before optimisation.

Satisfactory certificates of analysis of the test and reference product are presented

Population(s) studied

34 healthy subjects (19 male and 15 female, 19-44 years, 32 Caucasians and 2 Negroid) participated in the study. All 34 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Analytical methods

The samples were received frozen at the analytical facility and stored at -20±10°C until analysis.
The blood samples were analyzed by HPLC/MS/MS method for detection of metoprolol.
The analytical method has been validated.

Pharmacokinetic Variables

Method of assessment of pharmacokinetic parameters: Statistical and pharmacokinetic analyses were generated using Kinetic, version 5.1.3 and SAS version 9.1 (Mixed procedure).

Choice of primary variables and secondary PK variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{t/\infty}$, C_{max}, t_{max}, K_{el} and $t_{\frac{1}{2}\,el}$.
Primary variables: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}

Statistical methods

ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
The ANOVA model included sequence, subject nested within sequence, period and treatment.
Nonparametric test was carried out on t_{max}.

Criteria for conclusion of bioequivalence:

The 90% confidence interval for the exponential of the difference between the test and reference product for the ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ should be within 80-125%.

Results

Pharmacokinetic Parameters

Metoprolol (n=34)

PARAMETER	TEST		REFERENCE	
	MEAN	C.V.	MEAN	C.V.
C_{max} (ng/mL)	59.39	49.8	57.06	48.8
ln (C_{max}) (ng/mL)	3.9515	13.8	3.9106	14.2
T_{max} (hours) *	6.00	33.8	6.00	33.8
AUC_T (ng·h/mL)	1142.81	57.8	1121.87	57.3
ln (AUC_T) (ng·h/mL)	6.8676	9.2	6.8557	9.0
AUC_∞ (ng·h/mL)	1171.27	56.9	1154.30	57.4
ln (AUC_∞) (ng·h/mL)	6.9024	8.8	6.8933	8.6
$AUC_{T/\infty}$ (%)	96.63	3.2	96.38	3.7
K_{el} (hour^{-1})	0.1047	22.9	0.1037	22.5
$T\frac{1}{2}_{el}$ (hours)	7.00	25.5	7.05	24.5

* median is presented

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE		LOWER	UPPER
C_{max}	52.01	49.93	104.17	97.67	111.09
AUC_T	960.65	949.28	101.20	96.43	106.20
AUC_∞	994.64	985.63	100.91	96.19	105.87

The 90% confidence interval for the ln-transformed primary variables C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ is within the acceptance range of 80-125%.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study the initially developed metoprolol succinate prolonged release tablets are considered bioequivalent with Beloc-Zok/Selo-Zok forte prolonged release tablets, AstraZeneca after single-dose administration in fed conditions.

BE study 3 - Multiple-dose, fasting conditions

Study design
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, multiple dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two period. In each period 190 mg was administered in the morning for 6 consecutive days in each period.

The subjects were fasted overnight for at least 10 hours prior to the first drug administration. For the first five doses, a light breakfast was served 0.5 hour following drug administration. A standardised lunch, a supper and a light snack were served at least 4 hours and approximately 10 and 13 hours, respectively, after drug administration. Water was allowed *ad libitum*.
For the last, 6th, drug administration the subjects fasted overnight for at least 10 hours before drug administration. Standardised meals/snack was served 4, 10 and 13 hours after drug administration. Water was allowed *ad libitum* until 2 hours pre-dose and 2 hours after drug administration.

Blood samples were collected prior to the first drug administration and within 5 minutes of the 4th, 5th and 6th drug administration and at time points up to 24.0 hours after the 6th drug administration.
Each drug administration consisted of a 190 mg prolonged release tablet with 240 ml of water for the analyses of metoprolol.

Test and reference products
Metoprolol succinate 190 mg prolonged release tablets have been compared to Beloc-Zok forte 190 mg prolonged release tablets by AstraZeneca from the German market. The batch of the test product is the initially developed formulation before optimisation.

Satisfactory certificates of analysis of the test and reference product are presented.

Population(s) studied
40 healthy subjects (36+4 standby) (28 male and 12 female; 34 Caucasian, 1 Mongoloid and 5 Negroid; 20-45 years) participated in the study. 37 subjects completed the study. As per protocol the first 36 subjects completing the study were analysed and included in the statistical analysis.

Analytical methods
The samples were received frozen at the analytical facility and stored at -20±10°C until analysis.
The blood samples were analyzed by HPLC/MS/MS method for detection of metoprolol.
The analytical method has been validated.

Pharmacokinetic Variables
Method of assessment of pharmacokinetic parameters: Statistical and pharmacokinetic analyses were generated using Kinetic, version 5.2.0 and SAS version 9.1 (Mixed procedure).

Choice of primary variables and secondary PK variables:
The parameters calculated were C_{max}, C_{min}, AUC_τ, C_{pd} (trough - or pre-dose conc.), t_{max} and fluctuation.
Primary variables: C_{max}, C_{min} and AUC_τ.

Statistical methods
Parametric ANOVA was performed on C_{max}, C_{min}, C_{pd}, T_{max}, AUC_τ and Fluctuation; geometric confidence interval was calculated for C_{max}, C_{min}, and AUC_τ based on ln-transformed data; T_{max} was rank transformed.
The ANOVA model included sequence, subject nested within sequence, period and treatment.
Nonparametric test was carried out on t_{max}.

Criteria for conclusion of bioequivalence:
The 90% confidence interval for the exponential of the difference between the test and reference product for the ln-transformed parameters C_{max}, C_{min} and AUC_τ should be within 80-125%.
A widening of the acceptance range for C_{min} to 75-133% has been proposed in the study report. A post-hoc widening of the 90% CI is not acceptable, however, taking into account the additional multiple study dose performed, where the acceptance criteria for all primary variables were perfectly met, no issues will be raised on this ground.

Results

Pharmacokinetic Parameters

Metoprolol (n=36)

PARAMETER	TEST		REFERENCE	
	MEAN	C.V.	MEAN	C.V.
C_{min} (ng/mL)	38.72	76.9	47.45	77.2
ln (C_{min}) (ng/mL)	3.3532	25.7	3.5552	24.2
C_{max} (ng/mL)	121.55	57.2	123.49	56.3
ln (C_{max}) (ng/mL)	4.6236	14.1	4.6313	14.7
T_{max} (hours) *	5.50	17.8	6.00	38.9
AUC_τ (ng·h/mL)	1829.12	63.9	2017.02	63.0
ln (AUC_τ) (ng·h/mL)	7.2969	9.8	7.3913	9.8
Fluctuation (%)	119.12	25.8	113.45	119.2
ln(Fluctuation) (%)	4.7469	5.6	4.5329	10.9
Cpd_0 (ng/mL)	42.74	74.4	52.08	70.7
Cpd_{24} (ng/mL)	42.69	71.5	49.55	80.2
Cpd_{48} (ng/mL)	40.83	75.7	49.36	77.6

* median is presented

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS	
	TEST	REFERENCE		LOWER	UPPER
C_{min}	28.34	34.90	81.18	75.49	87.31
C_{max}	101.70	102.47	99.24	88.15	111.73
AUC_τ	1471.59	1614.22	91.16	86.65	95.91

The 90% CI for the ln-transformed C_{max} and AUC_τ are within the acceptance range of 80-125%, whereas the 90 CI for the ln-transformed C_{min} is within the widened acceptance limits of 75-133%.

Pharmacokinetic conclusion
Based on the results of the study bioequivalence has not been indisputably shown. However, when taking into consideration the recently performed additional multiple-dose study carried out with the formulation intended for marketing, bioequivalence is considered demonstrated.

Based on the submitted bioequivalence study metoprolol succinate prolonged release tablets are considered bioequivalent with Beloc-Zok/Selo-Zok forte prolonged release tablets, AstraZeneca after multiple-dose administration, when the results are supported by the additional study carried out.

BE study 4 - Multiple dose

Study design
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, multiple dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two period. In each period 190 mg was administered in the morning for 6 consecutive days in each period.

The subjects were fasted overnight for at least 10 hours prior to the first drug administration. For the first five doses, a light breakfast was served 0.5 hour following drug administration. A standardised lunch, a supper and a light snack were served at least 4.5 hours and approximately 10 and 13 hours, respectively, after drug administration. Water was allowed *ad libitum*.
For the last, 6th, drug administration the subjects fasted overnight for at least 10 hours before drug administration. Standardised meals/snack was served 4, 10 and 13 hours after drug administration. Water was allowed *ad libitum* until 2 hours pre-dose and 2 hours after drug administration.

Blood samples were collected prior to the first drug administration and within 5 minutes prior to the 4th, 5th and 6th drug administration and at time points up to 24.0 hours after the 6th drug administration. Each drug administration consisted of a 190 mg prolonged release tablet with 240 ml of water for the analyses of metoprolol.

Test and reference products
Metoprolol succinate 190 mg prolonged release tablets have been compared to Beloc-Zok forte 190 mg prolonged release tablets by AstraZeneca from the German market. The test product is the same formulation as intended for marketing and manufactured at the site applied for.

Satisfactory certificates of analysis of the test and reference product are presented.

Population(s) studied
40+4 healthy 22 male and 22 female subjects (36 White, 7 Black and 1 Asian; 20-45 years) participated in the study. 38 subjects completed the study and were used for the pharmacokinetic and statistical analysis.

Analytical methods
The samples were received frozen at the analytical facility and stored at -20±10°C until analysis.
The blood samples were analyzed by HPLC/MS/MS method for detection of metoprolol.
The analytical method has been validated.

Pharmacokinetic Variables
Method of assessment of pharmacokinetic parameters: Statistical and pharmacokinetic analyses will be carried out using Kinetic and SAS (version 9.1.3 or higher) using the Mixed procedure.

Choice of primary variables and secondary PK variables:
The parameters calculated were C_{max}, C_{min}, AUC_{τ}, C_{pd} (trough - or pre-dose conc.), t_{max} and fluctuation.
Primary variables: C_{max}, C_{min} and AUC_{τ}.

Statistical methods

Parametric ANOVA was performed on C_{max}, C_{min}, T_{max}, AUC_τ and Fluctuation; geometric confidence intervals were calculated for C_{max}, C_{min} and AUC_τ, based on ln-transformed data; T_{max} was rank-transformed.

The ANOVA model included as fixed factors: sequence, period, treatment and as random factor: subject (nested within sequence).

Criteria for conclusion of bioequivalence:

The 90% confidence interval for the exponential of the difference between the test and reference product for the ln-transformed parameters C_{max} and AUC_τ should be within 80-125% and for ln-transformed C_{min} it should be within 75-133%.

A widening of the 90% CI for C_{min} to 75-133% has been proposed. The widening of the 90% CI for C_{min} is not considered acceptable; however, since the results of the study are also with the acceptance range of 80-125%, no issue will be raised.

Results

Pharmacokinetic Parameters

Metoprolol

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{min} (ng/mL)	42.99	102.0	48.77	102.7
ln (C_{min}) (ng/mL)	3.3212	30.7	3.4073	30.7
C_{max} (ng/mL)	141.18	60.2	134.73	64.3
ln (C_{max}) (ng/mL)	4.7849	12.3	4.7128	13.3
T_{max} (hours) *	6.00	34.4	7.00	41.6
AUC_τ (ng·h/mL)	5666.45	85.4	6403.82	85.6
ln (AUC_τ) (ng·h/mL)	8.3560	9.1	8.4748	9.0
Fluctuation (%)	53.44	44.3	41.00	42.4
ln (Fluctuation) (%)	3.9026	9.9	3.6417	10.4
Cpd_{-48} (ng/mL)	38.61	95.6	44.88	95.9
Cpd_{-24} (ng/mL)	41.69	94.2	51.13	93.1
Cpd_0 (ng/mL)	47.52	94.0	53.98	96.8
Cpd_{+24} (ng/mL)	45.26	99.7	53.17	95.9

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{min}	28.5	27.65	29.99	92.19	82.71	102.75
C_{max}	12.3	119.69	111.44	107.40	102.43	112.61
AUC_τ	15.6	4254.66	4801.55	88.61	83.44	94.10
Fluctuation	15.4	49.52	38.16	129.78	122.31	137.71

* units are ng/mL for C_{min} and C_{max}, ng·h/mL for AUC_τ, and % for Fluctuation

The 90% CI for all the primary variables C_{min}, C_{max} and AUC_τ after ln-transformation are within the acceptance limits of 80-125%. The fluctuation was higher for the test product than for the reference

and the 90% CI for fluctuation was not within 80-125%; however, this is not a primary variable for conclusion of bioequivalence and therefore of no concern for the overall conclusion of the study.

BE study 5 - Single dose, fasting conditions

Study design
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 190 mg was administered in each period.

The subjects were fasting overnight for at least 10 hours before drug administration and for at least 4 hours thereafter. Water was allowed *ad libitum* until 2 hours pre-dose and from 2 hours after drug administration. Standardised meals were served at appropriate times during the study.
The subjects were housed at the clinic until the 36-hours blood-draw and returned to the clinic for the last 48-hour blood-draw.

Blood samples were collected pre-dosing and at time points up to 48.0 hours post administration of a single-dose 190 mg prolonged release tablet with 240 ml of water for the analyses of metoprolol.

Test and reference products
Metoprolol succinate 190 mg prolonged release tablets have been compared to Beloc-Zok forte 190 mg prolonged release tablets by AstraZeneca from the German market. The composition of the test product used for the bioequivalence study is the same as applied for.

Satisfactory certificates of analysis of the test and reference product are presented.

Population(s) studied
36 subjects were planned to be included in the study and 35 was actually included.
Of these 35 subjects 21 were males and 14 female, 31 were Caucasians, 3 Black and 1 Asian, age: 19-44 years.
34 subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Analytical methods
The samples were received frozen at the analytical facility and stored at -20±10°C until analysis.
The blood samples were analyzed by HPLC/MS/MS method for detection of metoprolol.
The analytical method has been validated.

Pharmacokinetic Variables
Method of assessment of pharmacokinetic parameters: Statistical and pharmacokinetic analyses were generated using Kinetic, version 8.00 and SAS version 9.1 (Mixed procedure).

Choice of primary variables and secondary PK variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{t/\infty}$, C_{max}, t_{max}, K_{el} and $t_{\frac{1}{2}\ el}$.
Primary variables: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}

Statistical methods
ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
The ANOVA model included sequence, subject nested within sequence, period and treatment.
Nonparametric test was carried out on t_{max}.

Criteria for conclusion of bioequivalence:
The 90% confidence interval for the exponential of the difference between the test and reference product for the ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ should be within 80-125%.

Results

Pharmacokinetic Parameters

Metoprolol

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	76.31	87.8	77.66	91.7
$\ln(C_{max})$	4.0491	18.4	4.0629	18.2
T_{max} (hours) *	6.00	41.3	12.00	34.1
AUC_T (ng·h/mL)	1629.04	112.6	1727.72	107.3
$\ln(AUC_T)$	6.9669	12.9	7.0754	11.7
AUC_∞ (ng·h/mL)	1749.83	118.1	1831.92	113.3
$\ln(AUC_\infty)$	7.0252	12.7	7.1176	11.7
$AUC_{T/\infty}$ (%)	94.47	5.1	95.94	3.8
K_{el} (hour^{-1})	0.0855	28.9	0.1044	29.7
$T\frac{1}{2}_{el}$ (hours)	8.79	28.8	7.25	31.7

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	18.4	58.04	58.58	99.08	91.90	106.82
AUC_T	20.0	1074.71	1192.68	90.11	83.06	97.75

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

The 90% confidence interval for the ln-transformed primary variables C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ is within the acceptance range of 80-125%.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study metoprolol succinate prolonged release tablets are considered bioequivalent with Beloc-Zok/Selo-Zok forte prolonged release tablets, AstraZeneca after single-dose administration in fasting conditions.

BE study 6 - Single dose, fed conditions

Study design
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fed conditions with a wash out period of 7 days between the two administrations. 190 mg was administered in each period.

After an overnight fast for at least 10 hours the subjects received a standardised high-fat, high calorie meal 30 minutes before drug administration. Water was allowed *ad libitum* until 2 hours pre-dose and from 2 hours after drug administration. A standardised meal was served at least 4 hours after drug administration and at appropriate times thereafter during the study.
The subjects were housed at the clinic until the 36-hours blood-draw and returned to the clinic for the last 48-hour blood-draw.

Blood samples were collected pre-dosing and at time points up to 48.0 hours post administration of a single-dose 190 mg prolonged release tablet with 240 ml of water for the analyses of metoprolol.

Test and reference products
Metoprolol succinate 190 mg prolonged release tablets have been compared to Beloc-Zok forte 190 mg prolonged release tablets by AstraZeneca from the German market. The composition of the test product used for the bioequivalence study is the same as applied for.

Satisfactory certificates of analysis of the test and reference product are presented.

Population(s) studied
36 subjects were planned to be included in the study and 35 was actually included.
Of these 35 subjects 19 were males and 16 female; 34 were White and 1 Black; age: 20-45 years.
32 subjects completed the study and 31 subjects were included in the pharmacokinetic and statistical analysis.

Analytical methods
The samples were received frozen at the analytical facility and stored at -20±10°C until analysis.
The blood samples were analyzed by HPLC/MS/MS method for detection of metoprolol.
The analytical method has been validated.

Pharmacokinetic Variables
Method of assessment of pharmacokinetic parameters: Statistical and pharmacokinetic analyses were generated using Kinetic, version 8.0 and SAS version 9.1 (Mixed procedure).

Choice of primary variables and secondary PK variables:
The parameters calculated were AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{t/\infty}$, C_{max}, t_{max}, K_{el} and $t_{\frac{1}{2}\,el}$.
Primary variables: AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

Statistical methods
ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
The ANOVA model included sequence, subject nested within sequence, period and treatment.
Nonparametric test was carried out on t_{max}.

Criteria for conclusion of bioequivalence:
The 90% confidence interval for the exponential of the difference between the test and reference product for the ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ should be within 80-125%.

Results

Pharmacokinetic Parameters

Metoprolol

PARAMETER	TEST		REFERENCE	
	MEAN	**C.V. (%)**	**MEAN**	**C.V. (%)**
C_{max} (ng/mL)	96.73	76.3	83.43	65.0
$\ln (C_{max})$	4.2919	18.2	4.2027	16.7
T_{max} (hours) *	7.00	36.9	7.00	43.6
AUC_T (ng·h/mL)	1917.98	91.0	1815.81	87.3
$\ln (AUC_T)$	7.1783	12.6	7.1441	12.4
AUC_∞ (ng·h/mL)	2004.20	92.5	1905.65	91.7
$\ln (AUC_\infty)$	7.2259	12.3	7.1842	12.3
$AUC_{T/\infty}$ (%)	95.48	4.8	96.15	4.0
K_{el} (hours^{-1})	0.0919	24.8	0.1009	23.6
$T_{\frac{1}{2}el}$ (hours)	7.96	23.3	7.29	27.4

* median is presented

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	**REFERENCE**		**LOWER**	**UPPER**
C_{max}	17.0	73.81	67.73	108.98	101.31	117.23
AUC_T	12.6	1326.29	1285.45	103.18	97.71	108.95

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

The 90% confidence interval for the ln-transformed primary variables C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ is within the acceptance range of 80-125%.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study metoprolol succinate prolonged release tablets are considered bioequivalent with Beloc-Zok/Selo-Zok forte prolonged release tablets, AstraZeneca after single-dose administration in fed conditions.

Overall conclusion on bioequivalence
The application contains an adequate review of published clinical data.
A sufficient justification for the biowaiver for the three lower strengths (23.75, 47.5 and 95 mg) has been provided.
The additional information on the clinical aspects is found sufficient and bioequivalence between the test and reference product has been demonstrated after single dose administration under fasting and fed conditions and after multiple dosing; therefore, the metoprolol prolonged release tablets are found bioequivalent with the reference product.

V.   OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the generic product and the innovator are interchangeable. The benefit risk is, therefore, considered to be positive.

The following commitments have been made during the procedure:

- The Applicant commits to provide the validation reports of the first three industrial scale batches for each strength before market launch. The Applicant confirms that all validation batches will be manufactured using individual manufactured batches of coated granulate.
  The batch size of the first commercial scale batches will be:
    - 1,520,000 tablets for the 23.75 mg strength,
    - 760,000 tablets for the 47.5 mg strength,
    - 380,000 tablets for the 95 mg strength,
    - 190,000 tablets for the190 mg strength.

- The Applicant commits to test breakability (uniformity of mass of the tablet halves as per Ph. Eur. monograph 07/2007:0478) at each stability point concerning all batches included in the stability study:

    - For batches currently placed in stability, the remaining stability points to be tested are 24 and 36 months at 25ºC/60%RH.

    - For commercial batches, breakability test (uniformity of mass of the tablet halves as per Ph. Eur. monograph 07/2007:0478) will be tested at each stability point in all storage conditions (25ºC/60%RH, 30ºC/65%RH, and 40ºC/75% RH).