

## ***A comparative bioequivalence study of two prolonged-release metoprolol preparations***

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### **Abstract**

**Introduction.** Extended release metoprolol formulations display a reduced rate of absorption and a more uniform release characterized by lower peaks, longer time to peak and smaller peak to trough variation, and this allows for convenient once daily administration. A major advantage of extended release metoprolol formulations lies in the higher cardio-selectivity of lower rather than higher metoprolol plasma concentrations. In addition, the lower peak plasma concentrations tend to reduce adverse effects and, therefore, improve patient compliance.

Bioavailability of a generic (Beto ZK, Sandoz GmbH) and a brand name (Betoloc ZOK, AstraZeneca AB) extended-release metoprolol preparation was investigated using both *in vitro* and *in vivo* studies to determine if these two formulations were bioequivalent and, thus, safe and interchangeable. **Material and methods.** *Release profiles: Dissolution tests measuring the release of active substance from prolonged-release metoprolol preparations were carried out according to the European Pharmacopoeia (Ph. Eur.) specifications using a release apparatus with paddle mixer (apparatus 2), in a phosphate buffer at pH 6.8. Single dose bioequivalence study:* An open, randomized, 2-way crossover study comparing metoprolol succinate 47.5 mg from modified-release tablets between the Sandoz and AstraZeneca formulations was conducted in healthy volunteers under fasting conditions. *Steady state bioequivalence study:* A multiple dose study was conducted to compare the steady state pharmacokinetics between the Sandoz and AstraZeneca formulations. This study was an open, randomized, 2 periods, 2-way crossover study between Sandoz metoprolol succinate 190 mg modified-release tablets and AstraZeneca 190 mg modified-release tablets administered as multiple oral doses under fasting conditions in healthy volunteers. **Results.** *In vitro* dissolution tests, using identical methods to those described by Sieradzki *et al.* [1], showed similar dissolution profiles between Betoloc ZOK (AstraZeneca) and Beto ZK (Sandoz) according to the  $f_2$  similarity factor test. Furthermore, *in vivo* single dose and steady state clinical studies demonstrated bioequivalence between the two formulations as judged by AUC,  $C_{max}$  and  $t_{max}$ . Finally, none of the AstraZeneca batches tested in this study were capable of yielding a complete release profile at 20 h as reported by Sieradzki *et al.* [1]. **Conclusions.** The cumulative *in vitro* and *in vivo* results reported in this investigation show that the Sandoz and AstraZeneca formulations are bioequivalent, and the contradicting results reported by Sieradzki *et al.* [1] can best be explained by the use of an AstraZeneca batch that may have been on the borderline of specifications. *Geriatrics 2012; 6: 34-40.*

*Keywords:* ?????

### **Introduction**

Bioavailability is defined as the fraction of unchanged drug that reaches the systemic circulation and is dependent on the rate and extent of absorption. The therapeutic effect of a drug is generally dependent

on the concentration of that drug in the circulation and how quickly and for how long the drug is absorbed. Extended release formulations have allowed for a reduced rate of absorption and a more uniform release of the drug product resulting in a more constant blood plasma level compared to immediate release

formulations. The reduction in the large changes in plasma levels using extended release formulations often results in less side effects, and patient compliance is enhanced due to reduced frequency of administration. This is also the case with extended release metoprolol formulations. In addition, higher cardio-selectivity is also achieved with lower rather than higher metoprolol plasma concentrations, because selective  $\beta_1$ -receptor-blockers are not completely  $\beta_1$ -selective [2].

The pharmacokinetics of metoprolol, its tartrate and succinate salts, and its various formulations have been thoroughly described in relevant review articles, monographs and standard works [3-16]. Metoprolol is almost completely absorbed after oral administration. Only negligible amounts of metoprolol are absorbed in the stomach, and the duodenum, jejunum, ileum and colon have similar capacities for absorption by first-order kinetics [17-19]. Regional absorption decreases in anatomical order with approximately two-thirds of the amount of metoprolol leaving the stomach being absorbed in the duodenum [20].

The systemic bioavailability varies considerably (range in healthy volunteers is 30 to 75%) owing to extensive presystemic metabolism in the liver. However, due to the large therapeutic window and common individual dose adjustments, these differences among subjects are not clinically relevant. Peak plasma concentrations are achieved within 2 to 3 hours after drug administration [4,7], and bioavailability may be increased (average 40% increase in AUC) by food intake [15,21]. Metoprolol is known for its high intersubject variability. For any given dose, there is a 10-20 fold variation in total plasma concentration between individuals as a consequence of presystemic metabolism, which ranges from 5% to 50% or more [8].

Metoprolol is rapidly and widely distributed throughout the body, with a high volume of distribution (Vd) of about 3 to 6 l/kg [4,7,15]. Metoprolol is not bound to plasma proteins to any appreciable extent [3] and is, therefore, dialyzable, as are its metabolites.

Metoprolol is extensively biotransformed predominantly by CYP2D6 in the liver with less than 5% of the drug eliminated unchanged by excretion in the urine after oral dosing [22]. Several pathways of metabolism have been described. Two of the metabolites, O-desmethylnmetoprolol and alpha-hydroxymetoprolol, are  $\beta_1$ -blocking agents, but they are substantially less potent than the parent drug and not considered

clinically relevant [23]. In general, lipophilic beta-blockers such as metoprolol are cleared by the liver and undergo hepatic first-pass metabolism. This results in the observed low bioavailability, interpatient variability in steady-state plasma drug concentrations, rapid elimination, and the possibility of drug interactions with other drugs that affect hepatic enzymes. In addition, the metabolism of metoprolol is subject to genetic polymorphism, and poor metabolizers, who constitute approximately 8% of a Caucasian population and 2% of most other populations, may develop very high plasma concentrations when given standard doses of metoprolol as a result of reduced presystemic metabolism [11,12,24,25].

The plasma half-life of metoprolol is approximately 3 to 7 hours [26]. Within the therapeutic range, the half-life is independent of dose and is unlikely to be affected by long-term treatment [8].

## Purpose of the study

The purpose of this report was to reassess the bioequivalence of Betaloc ZOK (AstraZeneca AB) and Beto ZK (Sandoz GmbH) containing 47.5 mg of metoprolol succinate as a result of a recent investigation [1] that reported differences between the release profiles of Betaloc ZOK and Beto ZK. A reassessment is relevant from a safety and efficacy perspective as both products have been approved by numerous European regulatory authorities and are considered to be bioequivalent and, therefore, fully interchangeable.

## Material and methods

*Release profiles:* Dissolution profiles measuring the release of active substance from prolonged-release metoprolol preparations (Betaloc ZOK and Beto ZK) were carried out according to the European Pharmacopoeia specifications using a releasing apparatus with a paddle mixer (apparatus 2), in a 0.05 M phosphate buffer at pH 6.8. Samples for similarity factor ( $f_2$ ) testing were taken at 4h, 12 h and 20 h.

### *Release parameters:*

Rotation speed: 100 rpm

Release fluid temperature: 37°C  $\pm$  0.5°C

Release fluid volume: 500 ml,

Number of tablets in each vessel: 1

Volume of sample (online measurement)

Phosphate buffer (0.05 M), pH 6.8 (prepared according to Ph. Eur.)

#### *Sample analysis:*

Samples and standard (pH 6.8 buffer) were measured at a wave length of 222 nm using a spectrometer and a 0.5 cm cuvette.

#### *Similarity of dissolution profiles:*

Assessment of similarity was performed according to CHMP Guideline on the Investigation of Bioequivalence [27] using the recommended  $f_2$  test.

*Single dose bioequivalence study*<sup>§</sup>: An open, randomized, 2-way crossover study comparing metoprolol succinate 47.5 mg modified-release tablets between the Sandoz and AstraZeneca formulations was conducted on healthy subjects under fasting conditions. Twenty-four healthy Caucasians (non-smokers, 19-45 years of age) were enrolled and randomised in accordance with the protocol. They were investigated according to a single-centre, open, 2-way within-subject crossover design, each time involving the administration of a single oral dose of metoprolol. Primary parameters were  $AUC_{0-t}$  and  $C_{max}$ . The design of the study was adequate to determine the pharmacokinetic parameters of the test (Sandoz) and the reference (AstraZeneca) formulations. The mean ratio of residual area was approximately 3%. Therefore, the chosen sampling period was long enough to allow an extrapolation of  $AUC_{0-t}$  to infinity. No carry over effect, no period effect and no treatment effect was observed. Bioequivalence of the two formulations was determined based on 90% CIs of the mean ratio of In-transformed  $AUC_{0-t}$  and  $C_{max}$ .

*Steady state bioequivalence study*<sup>§</sup>: The study was conducted to compare the steady state (multiple dose) pharmacokinetics between the Sandoz and AstraZeneca formulations. This study was an open, randomized, 2 periods, 2-way crossover bioequivalence study of metoprolol succinate 190 mg modified-release tablets administered as multiple oral doses of 190 mg under fasting conditions. Twenty-four healthy Caucasians (non-smokers, 19-55 years of age) were enrolled and randomised in accordance with the protocol. For safety reasons, phenotyping was performed to exclude low-metabolisers in order to avoid high plasma levels. Volunteers were inves-

tigated according to a single-centre, multiple-dose, open-label, 2-way within-subject crossover design, each time involving the administration of a daily oral dose of 190 mg metoprolol on 6 consecutive days. Concentrations in plasma were determined by using the LC/MS method. Primary parameters were  $AUC_{t,ss}$  and  $C_{max,ss}$ . Bioequivalence of the two formulations was determined based on 90% CIs of the mean ratio of In-transformed  $AUC_t$  and  $C_{max,ss}$ .

<sup>§</sup> Bioequivalence studies were conducted after the approval from the Ethics Review Committee (IRB Services, Ontario, Canada) and the Canadian Health Authorities. All clinical work was conducted in compliance with Good Clinical Practice rules (GCP), as referenced in the ICH guidelines (ICH E6), Good Laboratory Practices, local regulatory requirements, and the principles enunciated in the Declaration of Helsinki (Edinburgh, Scotland, 2000).

## Results and discussion

Dissolution profiles for testing similarity were carried out at pH 6.8 (0.05 M buffer, prepared according with Ph. Eur.) from 12 randomly selected tablets for the following brands:

- Betaloc ZOK 50 mg prolonged-release tablets, batch no. MH4363 (AstraZeneca AB)
  - Beto ZK 50 mg prolonged-release tablets, batch no. BE5418 (Sandoz GmbH)
- both containing 47.5 mg metoprolol succinate.

The criteria for  $f_2$  testing as stated in the current CHMP guideline [27] are as follows:

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of > 85% dissolved for any of the formulations
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point,

where an  $f_2$  value between 50 and 100 indicates that the two dissolution profiles are similar.

Sampling for the  $f_2$  test was performed at 4 h, 12 h and 20 h time points (table 1 and figure 1), and all criteria listed above could be met with respect to the

dissolution profiles performed, and an  $f_2$  value with statistical relevance could, therefore, be determined. The overall release was slightly lower for the Beto ZK formulation at all sampled time points and had somewhat higher relative standard deviation compared to the Betaloc ZOK formulation. Nevertheless, an  $f_2$  value of 61 was determined, indicating that the two dissolution curves are similar. Neither formulation displayed complete release at the 20 h time point, with the Betaloc ZOK formulation showing 87% dissolution and the Beto ZK showing 80% dissolution, a 7 percentage points difference between the two formulations. This 7 percentage points difference at the 20 h time point is not clinically relevant considering the pharmacokinetic and pharmacodynamic characteristics for metoprolol described earlier combined with the calculated  $f_2$  value indicating statistical similarity between the two formulations.

Table 1. Results of release [%] of active substance in phosphate buffer, pH 6.8 over 20 h for Betaloc ZOK (AstraZeneca batch no. MH4363) and Beto ZK (Sandoz batch no. BE5418) together with calculated  $f_2$  value for 4 h, 12 h and 20 h time points. SD = standard deviation, RSD = relative standard deviation

Tab.	Betaloc ZOK (AstraZeneca) batch no. MH4363			Beto ZK (Sandoz) batch no. BE5418		
	Amount of released active substance (%)					
	4h	12h	20h	4h	12h	20h
1	23	61	83	18	54	75
2	27	71	94	25	63	85
3	26	67	90	24	61	84
4	26	62	83	20	54	75
5	27	67	90	24	61	83
6	25	67	90	25	65	88
7	26	66	87	17	56	78
8	26	67	89	19	58	77
9	24	63	85	16	53	74
10	23	64	87	26	64	87
11	25	63	85	17	56	80
12	24	62	86	18	54	76
Average (%)	25	65	87	21	58	80
SD	1,4	3	3,3	3,7	4,4	5
RSD	5,6	4,5	3,8	18	7,5	6,3

f <sub>2</sub> -Test	Result of calculation with three time points:			Result, f <sub>2</sub>
	time [hours]			
	4	12	20	
				61

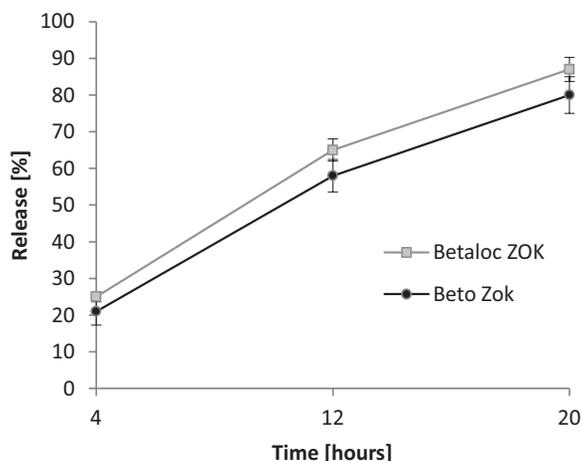


Figure 1. Graphical representation of dissolution data from table 1

Sieradzki *et al.* [1] previously reported 102% dissolution for the Betaloc ZOK (AstraZeneca) formulation at 20 h relative to 79.2% for the Beto ZK (Sandoz) formulation, and indicated that this difference could result in steady state differences if the tablet remained in the digestive tract for more than 20 h. This argument is plausible given the 20 percentage points difference that Sieradzki *et al.* [1] found between the two formulations in their investigation. To test whether the Betaloc ZOK batch that was used for our dissolution profile may have been a borderline batch, dissolution profiles were performed on two additional batches of the Betaloc ZOK formulation under the same conditions (table 2). Curiously, none of the Betaloc ZOK (AstraZeneca) batches that we tested displayed complete dissolution at the 20 h time point. It is unclear how Sieradzki *et al.* [1] could demonstrate complete dissolution of the Betaloc ZOK formulation at 20 h. However, it is worth noting that the 20 h dissolution of 79.2% for the Beto ZK (Sandoz) formulation reported by Sieradzki *et al.* [1] is quite consistent with the 20 h dissolution of 80% for the Beto ZK batch that we tested (table 1), indicating that our application of the methods used by Sieradzki *et al.* [1] were accurate. Given our results showing that none of the three different batches of the Betaloc ZOK formulation that we tested were capable of complete dissolution at 20 h, it is reasonable to consider that the Betaloc ZOK (AstraZeneca) batch used by Sieradzki *et al.* [1] may have been a borderline batch.

Table 2. Results of release [%] of active substance in phosphate buffer, pH 6.8 over 20 h for two additional Betaloc ZOK batches. SD = standard deviation, RSD = relative standard deviation

Tab.	Betaloc ZOK (Astra Zeneca) batch no. MH4392			Betaloc ZOK (Astra Zeneca) batch no. ML4442		
	Amount of released active substance (%)					
	4h	12h	20h	4h	12h	20h
1	28	74	94	31	73	95
2	26	73	95	30	69	90
3	25	70	92	28	72	94
4	27	71	92	29	70	93
5	26	71	92	27	66	87
6	26	70	91	25	67	89
Average (%)	26	72	93	28	70	91
SD	1	1,6	1,5	2,2	2,7	3,1
RSD	3,9	2,3	1,6	7,6	3,9	3,4

*In-vitro* dissolution profiles are often an unreliable surrogate of *in-vivo* bioequivalence, particularly in the absence of *in-vitro-in-vivo* correlation (IVIVC) data. Therefore, *in-vivo* bioequivalence (BE) studies were performed comparing the two formulations. An open, randomized, 2-way crossover, bioequivalence study comparing metoprolol succinate 47.5 mg modified-release tablets between the Sandoz and AstraZeneca formulations was conducted in healthy subjects under fasting conditions (see *Methods*), and the relevant pharmacokinetic parameters and study

results are summarised in table 3. Both the mean ratio of In-transformed  $AUC_{0-t}$  (93.02% to 107.85%) and  $C_{max}$  (99.63% to 117.65%) were within the acceptance range of 80% to 125% as stipulated in the current CHMP Guideline on the Investigation of Bioequivalence [27]. Based on the results, it can be concluded that the Sandoz metoprolol succinate modified release 47.5 mg formulation is bioequivalent in terms of rate and extent of absorption to the AstraZeneca formulation. Both formulations were equally tolerated, with no major side effects, and no relevant differences in safety profiles were observed between the two preparations, particularly with respect to the number or pattern of adverse events.

A multiple dose BE study was also conducted to compare the steady state pharmacokinetics between the Sandoz and AstraZeneca formulations (see *Methods*). Bioequivalence of the two formulations was determined based on 90% CIs of the mean ratio of In-transformed  $AUC_t$  and  $C_{max,ss}$ . As can be seen in table 4, the 90% CI of the mean ratio of In-transformed  $AUC_t$  (100.96% to 122.15%) and  $C_{max,ss}$  (91.12% to 113.50%) of the test (Sandoz) to reference (AstraZeneca) product were within the acceptance range of 80% to 125%. Therefore, it can be concluded that under steady-state conditions, the Sandoz and AstraZeneca metoprolol succinate modified release tablets are bioequivalent in terms of rate and extent of absorption. Both formulations were well tolerated, with no major side effects, and no relevant differences in safety profiles were observed, particularly in the number or pattern

Table 3. Sandoz formulation versus AstraZeneca formulation 47.5 mg metoprolol succinate - single dose bioequivalence study results

	$AUC_{0-t}$	$AUC_{0-inf}$	$C_{max}$
Ratio LS Means <sup>1</sup>	100.16%	98.91%	108.27%
90% Geometric C.I. <sup>2</sup>	93.02% to 107.85%	92.26% to 106.04%	99.63% to 117.65%
Intra-Subject CV	14.64%	13.77%	16.47%
Inter-Subject CV	79.36%	80.33%	68.09%

<sup>1</sup> calculated using least-squares means; <sup>2</sup> 90% geometric confidence interval using ln-transformed data

Table 4. Sandoz formulation versus AstraZeneca formulation 190 mg metoprolol succinate - multiple dose bioequivalence study results

	$AUC_t$	$C_{max,ss}$
Ratio LS Means <sup>1</sup>	111.05%	101.70%
90% Geometric C.I. <sup>2</sup>	100.96% to 122.15%	91.12% to 113.50%
Intra-Subject CV	17.81%	20.58%
Inter-Subject CV	47.06%	39.72%

<sup>1</sup> calculated using least-squares means; <sup>2</sup> 90% geometric confidence interval using ln-transformed data

of adverse events between the preparations also during multiple dose administration.

The multiple dose study is particularly relevant here as it shows that there is no steady state difference between the two formulations as Sieradzki *et al.* [1] had postulated based on their *in-vitro* dissolution results.

## Conclusions

The cumulative results of the *in-vitro* and *in vivo* data presented here clearly show that the Sandoz and AstraZeneca formulations are bioequivalent, and thus, safe and interchangeable. The limited and contradictory *in vitro* data presented in Sieradzki *et al.* [1] can best be explained by the use of a possible borderline Betaloc ZOK (AstraZeneca AB) batch used for the dissolution profile performed in their study. This could be due to variability in the manufacturing process. Additionally, improper handling by the testing laboratory or other unknown events cannot be ruled out. This seems to be the best possible explanation considering that we were unable to duplicate complete dissolution for three separate Betaloc ZOK (AstraZeneca AB) batches. However, the dissolution results that we obtained for the Beto ZK (Sandoz GmbH) formulation were consistent to those reported by Sieradzki

*et al.* [1], indicating that we accurately duplicated their dissolution protocol. Furthermore, we had no difficulty calculating an  $f_2$  value according to current CHMP guideline [27] for dissolution profile similarity testing, and the *in vivo* BE data presented here unequivocally demonstrate bioequivalence for the two formulations.

Generic drug companies produce medications that are just as safe and effective as their brand counterparts, and the prices for these generics are generally much lower. This translates into an ever growing increase in health and economic benefits across Europe as it allows national health care providers to cut costs while still providing the best possible health care to the most possible patients. This is particularly relevant in today's financial times, and it is important for health care professionals as well as lay people to realize the benefits to the public health when appropriate patents for brand name drugs have expired allowing lower priced and equivalent generic versions to become available.

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## References

1. Sieradzki E, Kwiatkowska B, Marzec A, Duda J, Król M, Izbicki L. Badanie porównawcze dostępności farmaceutycznej preparatów metoprololu o przedłużonym uwalnianiu. *Informator Lekarski* 2010;4:28-32.
2. Tafreshi MJ, Weinacker AB. Beta-adrenergic-blocking agents in bronchospastic diseases: a therapeutic dilemma. *Pharmacotherapy* 1999;19:974-8.
3. Ablad B, Borg KO, Carlsson E, Ek L, Johnsson G, Malmfors T, Regårdh CG. A survey to the pharmacological properties of metoprolol in animals and man. *Acta Pharmaco Toxicol* 1975; 36 Suppl V:7-23.
4. Ablad B, Borg KO, Carlsson E, Johnsson G, Regårdh CG. Metoprolol. *Pharmacol Biochem Prop Drug Subst* 1979;2:186-228.
5. AHFS. Drug Information - Metoprolol succinate / Metoprolol tartrate. Bethesda: American Hospital Formulary Service, American Society of Health-System Pharmacists, Inc. 2002;1672-80.
6. Benfield P, Clissold SP, Brogden RN. Metoprolol: An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in hypertension, ischaemic heart disease and related cardiovascular disorders. *Drugs* 1986;31:376-429.
7. Brogden RN, Heel RC, Speight TM, Avery GS. Metoprolol - A review of its pharmacological properties and therapeutic efficacy in hypertension and angina pectoris. *Drugs* 1977;14:321-48.
8. Cruickshank JK. The clinical importance of cardioselectivity and lipophilicity in beta blockers. *Am Heart J* 1980; 100(2):160-178.
9. Kendall MJ. Metoprolol - controlled release, zero order kinetics. *J Clin Pharm Ther* 1989;14:159-79.
10. Martindale - The complete drug reference. Metoprolol tartrate. 33rd ed. London: Pharmaceutical Press 2002. p. 931-2.
11. McDevitt DG. Comparison of pharmacokinetic properties of beta-adrenoceptor blocking drugs. *Eur Heart J* 1987; 8 Suppl M:9-14.
12. PDR - Physicians' Desk Reference Electronic Library. TOPROL XL - metoprolol succinate tablet, extended release AstraZeneca LP 2007.

13. Plosker GL, Clissold SP. Controlled release metoprolol formulations. A review of their pharma-codynamic and pharmacokinetic properties, and therapeutic use in hypertension and ischaemic heart disease. *Drugs* 1992; 43:382-414.
14. Prakash A, Markham A. Metoprolol: a review of its use in chronic heart failure. *Drugs* 2000;60:647-78.
15. Regårdh CG, Johnsson G. Clinical pharmacokinetics of metoprolol. *Clin Pharmacokin* 1980;5:557-69.
16. Sandberg A, Abrahamsson B, Regårdh CG, Wieselgren I, Bergstrand R. Pharmacokinetic and biopharmaceutic aspects of once daily treatment with metoprolol CR/ZOK: A review article. *J Clin Pharmacol* 1990;30:S2-S16.
17. Godbillon J, Gerardin A, John A, Theobald W. Comparative pharmacokinetic profiles of metoprolol and chlorthalidone administered alone or in combination to healthy volunteers. *Eur J Clin Pharmacol* 1983;24:655-60.
18. Jobin G, Cortot A, Godbillon J, Duval M, Schoeller JP, Hirtz J, Bernier JJ. Investigation of drug absorption from the gastrointestinal tract of man. I. Metoprolol in the stomach, duodenum and jejunum. *Br J Clin Pharmacol* 1985;19 Suppl 2:97S-105S.
19. Vidon N, Evard D, Godbillon J, Rongier M, Duval M, Schoeller P, Bernier JJ, Hirtz J. Investiga-tion of drug absorption from the gastrointestinal tract of man. II. Metoprolol in the jejunum and ileum. *Br J Clin Pharmacol* 1985;19 Suppl 2:107S-112S.
20. Hirtz J. The gastrointestinal absorption of drugs in man: a review of current concepts and methods of investigation. *Br J Clin Pharmacol* 1985;19 Suppl 2:77S-83S.
21. Melander A, Danielson K, Schersten B, Wålin E. Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin Pharmacol Ther* 1977;22:108-12.
22. Regårdh CG, Jordö L, Ervik M, Lundborg P, Olsson R, Rönn O. Pharmacokinetics of metoprolol in patients with hepatic cirrhosis. *Clin Pharmacokin* 1981;6:375-88.
23. Borg KO, Carlsson E, Hoffmann KJ, Jönsson TE, Thorin H, Wallin B. Metabolism of metoprolol-(3H) in man, the dog and the rat. *Acta Pharmacol Toxicol* 1975;36 Suppl V:125-35.
24. Lennard MS, Tucker GT, Silas JH, Woods HF. Debrisoquine polymorphism and the metabolism and action of metoprolol, timolol, propranolol and atenolol. *Xenobiotica* 1986;16:435-47.
25. Smith RL.  $\beta$ -Blockers and genetic polymorphism - Polymorphic metabolism of the  $\beta$ -adrenoreceptor blocking drugs and its clinical relevance. *Eur J Clin Pharmacol* 1985;28 Suppl:77-84.
26. Product Information: Toprol-XL, metoprolol succinate extended-release tablets. AstraZeneca LP 2010. Wilmington, DE, USA.
27. Committee for Medicinal Products for Human Use (CHMP). Guideline on the Investigation of Bioequivalence. January 2010. CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.