Public Assessment Report

Scientific discussion

Metoprolol Zentiva 25 mg
Metoprolol Zentiva 50 mg
Metoprolol Zentiva 100 mg
Metoprolol Zentiva 200 mg
prolonged-release tablets

metoprolol

SK/H/0298/001-004/DC

Date: 07.02.2025
Applicant: Zentiva, k.s., Czech Republic

This module reflects the scientific discussion for the approval of Metoprolol Zentiva. The procedure was finalised at 21.04.2024. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Metoprolol Zentiva 25 mg, Metoprolol Zentiva 50 mg, Metoprolol Zentiva 100 mg, Metoprolol Zentiva 200 mg, prolonged-release tablets, from Zentiva k.s., Czech Republic.

The product is indicated for*:*
Adults

- Hypertension: reduction of blood pressure and the risk of cardiovascular and coronary mortality (including sudden death), and morbidity.
- Angina pectoris.
- Symptomatic chronic mild to severe heart failure: as an adjunct to standart treatment of heart failure to prolong survival, reduce hospital stay, improve left ventricular function, improve NYHA grade of heart failure and improve quality of life.
- Cardiac arrhythmias, especially including supraventricular tachycardia.
- Maintenance treatment after myocardial infarction
- Functional heart disorders with palpitations.
- Prophylaxis of migraine.

Children and adolescents 6 − 18 years of age

- Treatment of hypertension.

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

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

With Slovakia as the reference member state in this decentralised procedure, the Applicant (Zentiva k.s., Czech Republic) applied for the marketing authorisation in RMS and CMSs: Czechia, Estonia, Latvia, Lithuania and Poland.

The reference medicinal product is Betaloc ZOK 25 mg, 50 mg and 100 mg prolonged-release tablets held by marketing authorisation holder Recordati Industria Chimica e Farmaceutica S.p.A., Italy and granted via national procedure in Slovakia (58/0330/00-S, 58/0033/99-S, 58/0034/99-S).
A European Reference Product (ERP) is used in RMS and CMS PL: Betaloc ZOK, 200 mg, prolonged-release tablets held by Herbacos Recordati s.r.o., registered in Czechia.

II. QUALITY ASPECTS

II.1 Introduction

Metoprolol Zentiva 25 mg:
White to off white, oval, biconvex film coated tablets with dimensions approx. 8.5 mm x 4.5 mm, debossed with C on one side and 69 on other side of break line and break line on other side. The tablet can be divided into equal doses.

Each prolonged-release tablet contains 23.75 mg metoprolol succinate equivalent to 25 mg metoprolol tartrate.

Metoprolol Zentiva 50 mg:
White to off white, oval, biconvex film coated tablets with dimensions approx. 12.0 x 6.0 mm, debossed with C on one side and 68 on other side of break line and break line on other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Each prolonged-release tablet contains 47.5 mg metoprolol succinate equivalent to 50 mg metoprolol tartrate.

Metoprolol Zentiva 100 mg:
White to off white, oval, biconvex film coated tablets with dimensions approx. 14.0 mm x 8.0 mm, debossed with C on one side and 67 on other side of break line and break line on other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Each prolonged-release tablet contains 95 mg metoprolol succinate equivalent to 100 mg metoprolol tartrate.

Metoprolol Zentiva 200 mg:
White to off white, oval, biconvex film coated tablets with dimensions approx. 18.5 mm x 9.5 mm, debossed with C on one side and 66 on other side of break line and break line on other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Each prolonged-release tablet contains 190 mg metoprolol succinate equivalent to 200 mg metoprolol tartrate.

The excipients used in this formulation (cellulose microcrystalline; ethyl cellulose; dibutyl sebacate; hypromellose; tributyl acetylcitrate; poly(vinyl acetate); talc; macrogol; povidone; lactose monohydrate; silica colloidal anhydrous; magnesium stearate; titanium dioxide (E171)) were chosen based on the results of a literature study, experience gained previously and to match the tablet weight to that of the reference product. The excipients used are all well established. The composition of the four strengths is quantitatively proportional

The finished product is packed into PVDC/PVC-Al blisters containing 30, 50, 100, 250 prolonged-release tablets.

II.2 Drug Substance

The drug substance *metoprolol succinate* is described in the European Pharmacopoeia monograph No.1448.

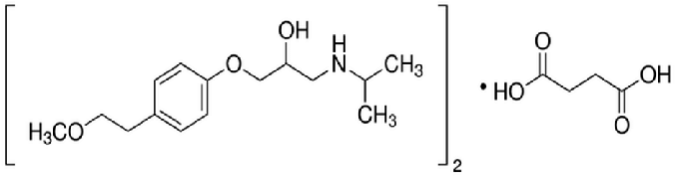
INN: Metoprolol Succinate

Chemical name:

2 - propanol, 1-[4 - (2 - Methoxyethyl)phenoxy] - 3 - [(1-Methylethyl)amino] – butanedioate OR (t) - 1 - (Isopropyl amino) - 3 - [p - 2 – methoxyethyl phenoxy] - 2 - propranol succinate OR bis[(2RS) 1 - [4 - (2 - methoxyethyl)phenoxy] - 3 - [(1-methyl - ethyl)amino]propan - 2 - 01]butanedioate.

Molecular Formula: $(C_{15}H_{25}NO_3)_2C_4H_6O_4$

Structural formula:



Isomerism: Metoprolol Succinate manufactured by Ipca is a racemic mixture.

The API is supplied by IPCS Laboratories Limited, India. Quality of the drug substance is covered by CEP (2004-028).
Specification for metoprolol succinate by DPM is set according to the current monograph No. 1448 with additional tests for residual solvents, particle size and nickel content.

The re-test period is 60 months if stored in double PE bags in either a fibre or a PE drum, as per the CEP.

II.3 Medicinal Product

Pharmaceutical development
The applicant's objective was to develop a generic product Metoprolol succinate prolonged-release tablets 190 mg, 95 mg, 47.5 mg and 23.75 mg to reference medicinal product Beloc-Zok 190 mg, 95 mg, 47.5 mg and 23.75 mg (marketing authorization holder AstraZeneca GmbH).
The aim was to develop a formulation using similar excipients or other excipients to reach stability of the formulation and to match the *in-vitro* dissolution profile and *in-vivo* bioequivalence.

The pharmaceutical development studies were conducted by drug product manufacturer Ipca Laboratories Ltd., Mumbai, India.

Development of drug product for EU market was in line with development of drug product for US market. Qualitative composition of both formulations for all strengths is the same. US product and EU product have the same quantitative composition till coated pellet stage. In order to make all strengths proportional, the extra-granular excipients quantity were increased in EU product (190 mg, 95 mg, 47.5 mg). So, composition of EU product is linear and proportional for all strengths.
All excipients used in the manufacture of the drug product comply with the current requirements of Ph. Eur., except dibutyl sebacate, silicified microcrystalline cellulose (Prosolv SMCC HD90), lactose monohydrate 75 parts and cellulose microcrystalline 25 parts (MicroceLac 100). In house specifications for these excipients are identical to those of manufacturer of excipients.

Manufacture of the product
Multi-unit particulate system (MUPS) for prolonged release dosage form was selected for manufacture of the drug product.
Manufacturing process for pellet-based approach consists of the following steps: seal coating, drug layering, ethyl cellulose coating, kollicoat coating, lubrication, lubricated blend bifurcation, compression, film coating and packaging.

The manufacturing flow chart was provided. The description of manufacturing process is provided in sufficient detail.

Product specification
The specification (release and shelf-life) for the drug product was provided by the drug product manufacturer. Specification is set in line with ICH Q6A and GL for modified release formulations.

Stability of the product
Based on stability results from long-term stability studies covering 24 months and accelerated studies covering 6 months, the approved shelf life of the drug product is 24 months in the primary container (PVDC / PVC-blister pack) with no special storage conditions.
Closure system
The drug product is packed in the PVDC/PVC blister with plain aluminium foil.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and finished product has been satisfactorily presented.
The quality of the product is considered acceptable when used in accordance with the conditions defined in the SmPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The Applicant provided both an incomplete ERA assessment and consumption data.
The consumption data did not show an increase from 2019 to 2021 in the EU member states:

	2018	2019	2020	2021	2018 vs 2019	2019 vs 2020	2020 vs 2021
AUSTRIA	147,27	2626,87	2520,03	2315,43	1784%	96%	92%
BELGIUM	1803,79	1679,45	1554,28	1467,23	93%	93%	94%
BULGARIA	19,15	3893,85	3751,82	3476,79	20332%	96%	93%
CROATIA	2,93	200,28	226,26	238,72	6845%	113%	106%
CZECH REPUBLIC	2144,31	11038,17	10643,54	10147,44	515%	96%	95%
ESTONIA	2016,63	1997,68	2078,87	1986,67	99%	104%	96%
FINLAND	233,75	3314,42	3178,56	2903,94	1418%	96%	91%
FRANCE	7205,21	7138,09	7007,94	6764,56	99%	98%	97%
GERMANY	133622,88	134000,27	133191,76	127707,43	100%	99%	96%
GREECE	7685,82	7653,48	7811,24	7653,84	100%	102%	98%
HUNGARY	129,58	5319,43	5036,44	4727,14	4105%	95%	94%
IRELAND	29,41	331,15	294,45	275,61	1126%	89%	94%
ITALY	14237,65	14648,04	15169,04	15412,47	103%	104%	102%
LATVIA	74,77	1214,45	1215,15	1135,00	1624%	100%	93%
LITHUANIA	182,75	3206,31	3505,91	3414,36	1754%	109%	97%
LUXEMBOURG	94,90	93,37	88,54	83,57	98%	95%	94%
NETHERLANDS	709,30	26408,50	26166,52	26042,41	3723%	99%	100%
POLAND	935,57	22600,72	23010,65	22208,14	2416%	102%	97%
PORTUGAL	536,32	520,44	507,27	476,52	97%	97%	94%
ROMANIA	207,36	19071,98	18623,90	17670,94	9198%	98%	95%
SLOVAKIA	96,28	3947,98	4006,13	4030,58	4101%	101%	101%
SLOVENIA	438,44	405,29	380,71	347,26	92%	94%	91%
SPAIN	1556,44	1516,14	1498,38	1480,05	97%	99%	99%
SWEDEN	303,93	13451,27	13346,91	13268,72	4426%	99%	99%
UK	158,01	1428,96	1160,98	1117,40	904%	81%	96%
NORWAY	195,77	6468,59	6422,66	6363,79	3304%	99%	99%
Grand Total	**174768,2**	**294175,2**	**292397,9**	**282716,0**	**168%**	**99%**	**97%**

As the consumption data did not show an increase from 2019 to 2021 in the EU member states, further action is not needed as this is a generic product intended for substitution.

Conclusions on studies:
Considering the above data, metoprolol is not expected to pose an additional risk to the environment.

III.3 Discussion on the non-clinical aspects

Submitted non-clinical data are adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Metoprolol succinate, is a beta1-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as prolonged-release tablets. Metoprolol succinate prolonged-release tablet has been formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval.

Metoprolol only exhibits insignificant membrane stabilising effect and has no agonist effect. Metoprolol reduces or blocks the stimulating effect of catecholamines (particularly released in case of physical or mental stress) on the heart. Metoprolol reduces tachycardia, decreases the cardiac output and the contractility and lowers the blood pressure.

IV.2 Pharmacokinetics

Biowaiver

The following regulatory requirements were fulfilled according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms EMA/CHMP/EWP/280/96 Rev1:
a) The pharmacokinetics is linear.
a) The pharmaceutical products are manufactured by the same manufacturing process.
b) The qualitative composition of the different strengths is the same.
c) The composition of the strengths is quantitatively proportional.
d) The formulations contain identical beads or pellets.
d) Appropriate in vitro dissolution data confirms the adequacy of waiving. When RSD was over 10 %, the Applicant calculated f2 by bootstrap f2 method as recommended.

Conclusion: the biowaiver criteria were fulfilled.

Bioequivalence studies

The applicant has submitted as report three bioequivalence studies:

- comparative, single-dose, open-label, randomised, two-period, cross-over, 2-treatment, 2-sequence bioequivalence study of two formulations of metoprolol succinate 190 mg prolonged release tablets under fasting conditions (study code BA19064027).
- comparative, single-dose, open-label, randomised, two-period, cross-over, 2-treatment, 2-sequence bioequivalence study of two formulations of metoprolol succinate 190 mg prolonged release tablets under fed conditions (study code BA19064028).
- comparative, multiple-dose, open-label, randomised, two-period, cross-over, 2-treatment, 2-sequence bioequivalence study of two formulations of metoprolol succinate 190 mg prolonged release tablets under fasting conditions (study code BA19064026).

Table 1. Pharmacokinetic parameters for Metoprolol Single dose, Fast

Parameters	Geometric Mean		% Ratio	90% Confidence Interval for Logtransformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
C_{max} (ng/mL)	**70.758**	**70.594**	**100.23**	**96.57**	**104.03**
AUC_{0-t} (ng.hr/mL)	**1 426.043**	**1 446.890**	**98.56**	**93.45**	**103.94**
AUC_{0-inf} (ng.hr/mL)	**1 441.722**	**1 461.040**	**98.68**	**93.55**	**104.09**

Table 2. Pharmacokinetic parameters for Metoprolol Single dose, Fed

	Geometric Mean	% Ratio	90% Confidence Interval for Logtransformed data

Parameters	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
C_{max} (ng/mL)	79.961	81.033	98.68	95.55	101.91
AUC_{0-t} (ng.hr/mL)	1 491.818	1 524.784	97.84	92.77	103.18
AUC_{0-inf} (ng.hr/mL)	1 513.860	1 547.088	97.85	92.67	103.33

Table 3. Pharmacokinetic parameters for Metoprolol Multiple dose, Fast

Parameters	Geometric Mean		% Ratio	90% Confidence Interval for Logtransformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
C_{maxss} (ng/mL)	109.230	106.968	102.11	98.33	106.05
C_{tauss} (ng/mL)	29.423	27.497	107.00	94.35	121.36
AUC_{tauss} (ng.hr/mL)	1 779.061	1 758.707	101.16	95.99	106.61

Table 2.1: Summary of Pharmacokinetic Data for Metoprolol (n=49)

Dose: 1 x 190 mg

PARAMETER	Test Product: Metoprolol Succinate PR tablets 190 mg		Reference Product: Beloc-zok® forte 190 mg (Metoprolol Succinate) Prolonged Release tablets 190 mg	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (ng/mL)	49	81.719 ± 41.078 (50.267)	49	82.003 ± 43.055 (52.505)
AUCt (ng/mL)*(hr)	49	1743.349 ± 1040.852 (59.704)	49	1778.031 ± 1118.843 (62.926)
AUCi (ng/mL)*(hr)	49	1766.036 ± 1065.511 (60.333)	49	1799.857 ± 1144.541 (63.591)
AUCτ (ng/mL)*(hr)	49	1396.247 ± 757.772 (54.272)	49	1429.035 ± 814.576 (57.002)
AUCτ/AUCi	49	81.867 ± 6.911 (8.442)	49	82.278 ± 6.351 (7.719)
AUC_%Extrap_obs	49	1.086 ± 0.927 (85.307)	49	0.966 ± 0.723 (74.794)
Kel (1/hr)	49	0.131 ± 0.024 (18.664)	49	0.133 ± 0.027 (20.046)
tHalf (hr)	49	5.469 ± 1.001 (18.308)	49	5.414 ± 1.018 (18.802)
Tmax (hr)^	49	7.000 (3.500 - 16.000)	49	7.500 (4.500 - 14.000)

(^) Tmax is presented as Median (Range)

Table 2.2: Test & Reference Geometric mean, Ratio, Intra-Subject CV (%), 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Metoprolol (n=49)

Pharmacokinetic parameter	Geometric mean				Ratio (%)	Intra-Subject CV (%)
	N	Test	N	Reference		
Cmax (ng/mL)	49	70.758	49	70.594	100.23	10.997
AUCt (ng/mL)*(hr)	49	1426.043	49	1446.890	98.56	15.787
AUCi (ng/mL)*(hr)	49	1441.722	49	1461.040	98.68	15.838
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria**		**Outcome of BE result**	
Cmax (ng/mL)	(96.57%;104.03%)		80.00% - 125.00%		Bioequivalent	
AUCt (ng/mL)*(hr)	(93.45%;103.94%)		80.00% - 125.00%			
AUCi (ng/mL)*(hr)	(93.55%;104.09%)		80.00% - 125.00%			

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Metoprolol Zentiva is considered bioequivalent with reference medicinal product BELOC-ZOK® (Metoprolol succinate) Prolonged Tablets, 23.75/47.5/95/190 mg of RECORDATI Industria Chimica e farmaceutica S.p.A., Italy.

The results of study BA19064027, BA19064028, BA19064026 with 190 mg formulation can be extrapolated to other strengths 23.75/47.5/95 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Beta-receptor blocker, selective
ATC code: C07AB02

Mechanism of action
Metoprolol is a beta1-selective receptor blocker, i.e. metoprolol affects the beta1-receptors of the heart in lower doses than needed to affect beta2- receptors in peripheral vessels and bronchi.

Metoprolol only exhibits insignificant membrane stabilising effect and has no agonist effect.

IV.4 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 Metoprolol Zentiva 25 mg, Metoprolol Zentiva 50 mg, Metoprolol Zentiva 100 mg, Metoprolol Zentiva 200 mg.

Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant.

Risk minimisation measures
The safety information in the proposed product information is aligned with the reference medicinal
product. No additional risk minimisation activities are proposed by the applicant.

IV.5 Discussion on the clinical aspects

Submitted clinical dossier was of sufficient quality. Submitted data supported the chosen legal basis "generic application". Bioequivalence between the test product Metoprolol Zentiva with the reference medicinal product Betaloc ZOK has been demonstrated based on provided data.

V. 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 test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

These were the applications for a marketing authorisation of a medicinal product for human use as it is defined in Article 10(1) (generic application) of the European Directive 2001/83/EC as amended.
Decentralised procedure according to Article 28(3) of Directive 2001/83/EC as amended with Slovak Republic acting as RMS.
The Applicant Zentiva, k.s., Czech Republic has submitted MAA under procedural number SK/H/0298/001-004/DC.

CMS were:
SK/H/0298/001-003/DC – Czechia, Estonia, Lithuania, Latvia, Poland
SK/H/0298/004/DC – Czechia, Poland

As reference medicinal product Betaloc ZOK 25 mg, 50 mg, 100 mg prolonged-release tablets held by Recordati Industria Chimica e Farmaceutica S.p.A., Italy was chosen. Marketing authorisation was granted via national procedure in SK on 31 October 2000 (25 mg strength) and on 19 May 1999 (50 mg and 100 mg strength) on the basis of Article 8(3) application.
A European Reference Product was used in RMS and CMS PL: Betaloc ZOK, 200 mg, prolonged-release tablets held by Herbacos Recordati s.r.o., registered in Czechia.

To support the applications, the applicant has submitted as report three bioequivalence studies.

The benefit/risk assessment is considered positive.
The dossier is generally well presented and all processes appear to be well controlled. The application is acceptable from the quality perspective.
There are no objections to the dossier of Metoprolol Zentiva from a non-clinical point of view. From the clinical perspective, submitted clinical data are adequate to support the indication.
SmPC, PIL and labelling are satisfactory.