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Public Assessment Report

Scientific discussion

Bisoprolol Xantis
Bisoprolol fumarate

SK/H/0183/001-003/DC

Date: June 2018

This module reflects the scientific discussion for the approval of Bisoprolol Xantis. The procedure was finalised at 30.04.2018. 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 *Bisoprolol Xantis 2.5 mg, 5 mg and 10 mg, tablets* from *Xantis Pharma Limited, Cyprus.*
The product is indicated in the treatment of*:*

- hypertension
- angina pectoris
- stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors and diuretics and optionally cardiac glycosides.

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.

II. QUALITY ASPECTS

II.1 Introduction

Bisoprolol Xantis 2.5 mg are yellow round flat tablets with a break line on one side, diameter 7 mm.
The tablet can be divided into equal doses.
Bisoprolol Xantis 5 mg are white round biconvex tablets with a break line, diameter 7 mm.
The tablet can be divided into equal doses.
Bisoprolol Xantis 10 mg are dark pink round flat tablets with a break line on one side and embossed „10“ on the other, diameter 7 mm.
The tablet can be divided into equal doses.
Tablets are packed in blisters OPA/Alu/PVC and sealed with Alu foil.

II.2 Drug Substance

Bisoprolol is a cardioselective β1-adrenergic receptor blockers, without significant intrinsic sympathomimetic activity in its therapeutic dosage range. Blockade of β1- adrenergic receptors results in a reduction of heart rate, cardiac output and systolic and diastolic blood pressure. Bisoprolol is used to treat high blood pressure (hypertension) and ischemic heart disease (angina pectoris) also it is used for secondary prevention of myocardial infarction and heart failure.
The drug substance bisoprolol fumarate is described in the European Pharmacopoeia monograph No. 1710. The control tests and specifications for drug substance product are adequately drawn up.
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 5 years is justified.

II.3 Medicinal Product

The aim of the development phase was to develop a solid dosage form for oral administration using a simple, robust and economical technology which can ensure good stability of drug product and essential similarity with the reference product.
Due to the chemical and physical properties of bisoprolol fumarate and the low mass of tablets, the direct compression method was chosen.
All manufacturing steps and processes and also the used equipment are commonly and widely used in the pharmaceutical industry.
Drug product manufacturer performs all manufacturing steps including primary and secondary packing, batch control and batch release.

The proposed container closure system for Bisoprolol Xantis tablets is OPA/Al/PVC foil formed to the required shape form by heat and covered by Al foil. The suitability of this pack has been confirmed by the stability studies.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 3 batches. The batch analysis results show that the finished products meet the specifications proposed.

The dissolution profiles of the reference Concor, Biso tablets (PRO.MED.CS Praha a.s.) used in BEQ study and three pilot batches of all strength of Bisoprolol Xantis tablets (Saneca Pharmaceutical a.s.) are similar.
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.

Proposed shelf life for drug product Bisoprolol Xantis 2.5 mg tablets, Bisoprolol Xantis 5 mg tablets and Bisoprolol Xantis 10 mg tablets is 3 years.
These medical products do not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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

III.2 Ecotoxicity/environmental risk assessment (ERA)

Environmental Risk Assessment (ERA)
Since Bisoprolol Xantis is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bisoprolol is a potent highly $beta_1$-selective-adrenoreceptor blocking agent without intrinsic stimulating and relevant membrane stabilising activity.
Pharmacotherapeutic group: beta blocking agents, selective, ATC code: C07AB07

IV.2 Pharmacokinetics

To support the application, the applicant has submitted as report 1 bioequivalence study:
- Open label, two-period, two-sequence, two-way crossover, controlled, randomized, single dose bioequivalence study of Biso 10 mg tablets (test formulation) vs. equal dose of Concor 10 mg film-coated tablets (reference formulation) in healthy male and female volunteers under fasting conditions. The results of the study show bioequivalence between test and reference product when administered under fasted condition.
Applicant submitted overview supporting the BCS-biowaiver for Bisoprolol Xantis. In this overview, following aspects are discussed: Active pharmaceutical ingredient characteristics, therapeutic index and toxicity, solubility, permeability, comparative dissolution of drug product.

Active pharmaceutical ingredient characteristics
Active substance used in both test and reference product is bisoprolol fumarate. It is a white or almost white, slightly hygroscopic powder very soluble in water (according to the Ph. Eur the solubility corresponds to more than 1000 mg/mL at 25°C), freely soluble in methanol. As a moderately strong

base with pKa value of 9.57, bisoprolol ionizes in acidic conditions and is thus higher soluble at lower pH values. Bisoprolol fumarate is a racaemic mixture. The pharmacological activity of bisoprolol is predominantly due to the S(-)-enantiomer whose adrenergic receptor blocking activity is 15– 40 times greater than that of the R(+)- enantiomer.

Therapeutic index and toxicity

Bisoprolol is usually well tolerated and compares favourably to other agents within the class of beta blockers. Its high selectivity reduces the risk of extra-cardiac adverse effects at the therapeutic dose range. Its lack of intrinsic sympathomimetic activity as well as membrane stabilizing activity are other contributing factors to the relatively modest toxicity potential of the drug.

Reports of overdose with bisoprolol as the only agent are scarce in literature. In one case report, 140 mg of bisoprolol (7 times the maximum therapeutic daily dose) was taken in a suicide attempt; the only observed overdose symptom was sinus bradycardia. The patient fully recovered after 36 hours. The SmPC of the original product cites a case where as much as 2000 mg (100 times the maximum therapeutic daily dose) of bisoprolol was ingested without a fatal outcome.

Individual sensitivity to the adverse effects of bisoprolol may however vary greatly among patients. Patients with chronic heart failure are especially vulnerable. Slow dose titration as described above is therefore mandatory in this population.

Preclinical studies including conventional safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenicity did not reveal any special hazards to humans. The therapeutic index of bisoprolol is relatively wide.

Solubility

The solubility experiments were conducted as follows: the amount of drug substance corresponding approximately to 1250 mg was dissolved in 250 mL of each media and kept at 37 °C under rotation of 150 rpm for 24 hours. The samples were then filtered and the dissolved amount was determined by the validated HPLC method. The results of the determination in 3 studied media (three replicates each, mean value reported) in the volume of 250 mL are presented in the table below. The results indicate that the dissolution of API was complete and that the highest dose of bisoprolol fumarate (20 mg) is easily dissolved in less than 250 ml of media.

Table 5 Dose/solubility volume for bisoprolol fumarate in various media

Medium	Initial pH	Final pH	Solubility (mg/mL)	Ratio D/S (ml) acceptance limit: ≤ 250 mL highest dose: 20 mg
Hydrochloric acid 0.1 M	1.2	1.4	5.3 mg/mL	3.8 mL
Phosphate buffer	4.5	4.9	5.1 mg/mL	3.9 mL
Phosphate buffer	6.8	6.8	5.2 mg/mL	3.9 mL

Permeability

In general, log P values between 0 and 3 constitute an optimal window for passive drug absorption. As described above, bisoprolol fumarate is equally soluble in water as in organic solvents, i.e. it is as hydrophilic as lipophilic. The logarithm of partition coefficient (log P) values reported in literature are between 1-2.

Bisoprolol mass balance and metabolic profile was reported in 1986 by Leopold et al. who concluded that the enteral absorption following the oral administration of (^{14}C)-bisoprolol was nearly complete. Total radioactivity was predominantly excreted by the kidneys. Half of the dose of unchanged bisoprolol was submitted to direct renal excretion. Less than 2% of total radioactivity was recovered in faeces.

In the second study, Leopold et al. (1986) determined the absolute bioavailability by the comparison of pharmacokinetic profiles after oral and intravenous administration of 10 mg of bisoprolol. The figure below presents the plasma concentration-time profiles of bisoprolol after single oral and intravenous administration to 12 healthy male subjects. Ratios of the oral/i.v. AUC0 and the oral/i.v. urinary recoveries were calculated as 0.91 ± 0.06 and 0.88 ±0.20, respectively, indicating a

bioavailability of 90%. Taking into account the nearly complete enteral absorption, the first-pass metabolism of bisoprolol was estimated to be no more than 10% of the dose.

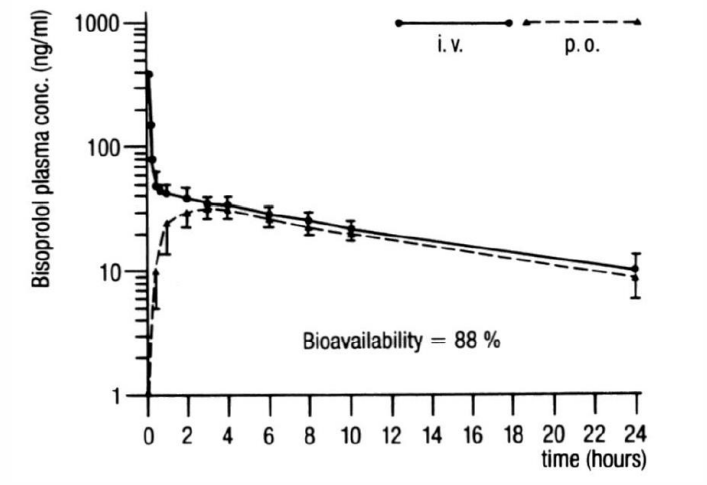

Figure 1 Mean plasma concetration time curves after i.v. and oral administration of 10 mg of bisoprolol (Leopold, 1986).

Comparative dissolution of drug product

A comparative study of dissolution profiles of two formulations (test and reference) as recommended by the Guideline was performed to demonstrate the similarity between the test and reference products under physiologically relevant experimental pH conditions.

Table 6 Experimental conditions of the comparative dissolution testing

Apparatus	I (basket)
Dissolution media	0.1M hydrochloric acid (pH 1.2) phosphate buffer (pH 4.5) phosphate buffer (pH 6.8)
Volume of medium	900 mL
Temperature	37°C ± 0.5°C
Agitation	100 rpm rotation speed
Temperature of medium	37±0.5°C
Number of units (capsules)	12
Sampling schedule	5, 10, 15, 20 and 30 minutes
Filtration	Full flow 2.7 µm filter
Method of evaluation	HPLC methodology

Three strengths were tested: 2.5, 5 and 10 mg. The test product were Bisoprolol Xantis 10 mg, 5 mg, 2.5 mg tablets from manufacturer Saneca Pharmaceuticals a.s., Slovakia. The reference products were Concor 5 mg and Concor 10 mg film-coated tablets and Concor Cor 2.5 mg film-coated tablets by Merck KgaA, Germany.

When comparing dissolution profiles of test and reference products of 10 mg strengths and 5 mg strengts, the dissolutions were more than 85 % in less than 15 minutes for all the products in all three pHs.

When comparing 2.5 mg strength of Bisoprolol Xantis and Concor Cor 2.5, dissolution profiles were as in the table below:

Table 10 Dissolution testing of Bisoprolol Xantis versus Concor® COR (strength 2.5 mg) at various pH (mean results)

Dissolution medium	Product	Batch number	Time in minutes / % dissolved amount				
			5	10	15	20	30
0.1 M Hydrochloric acid	Bisoprolol Xantis 2.5 mg	04180315	97.7	99.2	**98.9**	98.4	98.0
	Concor® COR 2.5 mg	18913	46.5	66.8	**79.7**	87.7	94.9
Phosphate buffer pH 4.5	Bisoprolol Xantis 2.5 mg	04180315	91.5	99.1	**99.2**	99.2	99.2
	Concor® COR 2.5 mg	18913	42.5	68.7	**79.7**	90.9	98.0
Phosphate buffer pH 6.8	Bisoprolol Xantis 2.5 mg	04180315	93.0	97.7	**98.0**	98.1	98.0
	Concor® COR 2.5 mg	18913	42.0	64.1	**77.7**	85.6	92.1

As can be seen from the results shown in table above, the dissolution of Concor COR 2.5 mg tablets is not as "very rapid" as observed with Concor higher strengths (less than 85% in 15 minutes at all pH conditions). The similarity of test versus reference product for the lowest strength (2.5 mg) was thus demonstrated by the comparison of two tablets of Bisoprolol Xantis 2.5 mg versus 1 tbl of Concor 5 mg. Under these conditions, more than 85% of bisoprolol was dissolved in less than 15 minutes from both products in all three pHs.

Excipients

The very rapid in vitro dissolution under discriminative conditions at all tested pH conditions indicates that gastric emptying rather than product performance is the rate-limiting step in bioavailability characteristics of both test and reference formulation.

Excipients contained in the test formulation (i.e. cellulose microcrystalline, crospovidone and magnesium stearate) were selected based on either the composition of the reference product, literature information or experience with similar formulations.

Microcrystalline cellulose is a filler widely used in oral pharmaceutical formulations. It is not absorbed systemically following oral administration. Crospovidone is a water-insoluble tablet disintegrant used conventionally at 2–5% w/w concentration. Magnesium stearate is among the most widely used lubricants, usually included at concentrations less than 1% w/w. Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations. All three above described excipients are contained in the reference product as well. It can be thus stated that the composition of both formulations is qualitatively similar.

As reported by Charoo et al. (2013), various excipients have been used in formulation of bisoprolol IR tablets. The list encompasses nearly 30 ingredients including those known to affect drug absorption, like mannitol and sodium laurylsulphate. Despite that, it can be assumed that all products listed successfully passed through the bioequivalence testing.

Overall, based on the results obtained in the bioequivalence study with Biso 10 mg manufactured by Promed by the same manufacturing process as Bisoprolol Xantis, the excipients used in the test do not affect the bioavailability of the product. In conclusion, all selected excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation nor any excipients known to affect bioavailability.

Conclusion on bioequivalence studies:

Based on the submitted bioequivalence studies Bisoprolol Xantis is considered bioequivalent with Concor COR 2.5 mg, Concor 5 mg and Concor 10 mg.

The justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

IV.3 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 generic medicinal products Bisoprolol Xantis 2.5 mg, 5 mg and 10 mg.

Safety specification

The summary of safety concerns approved in updated version 01.02 of the RMP:

Summary of safety concerns	
Important identified risks	Hypotension Bradycardia Bronchospasm in patients with bronchial asthma or obstructive airways disease Aggravation (worsening) of pre-existing heart failure Decreased diabetic control and masking of hypoglycaemic effects Syncope
Important potential risks	Renal failure Toxic skin reactions Fibrosis conditions (Peyronie´s disease, retroperitoneal fibrosis, pulmonary fibrosis) Interstitial lung disease / Interstitial pneumonitis Fatal hepatotoxicity
Missing information	Children and adolescents under 18 years of age

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

- Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP version 01.02

Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Important Identified Risks		
Hypotension	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: Section 4.3 Contraindications Section 4.5 Interactions with other medicinal products and other forms of interaction Section 4.8 Undesirable effects Section 4.9 Overdose Prescription only medicine Pack size	None proposed
Bradycardia	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk:	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Section 4.3 Contraindications Section 4.5 Interactions with other medicinal products and other forms of interaction Section 4.6 Fertility, pregnancy and lactation Section 4.8 Undesirable effects Section 4.9 Overdose Prescription only medicine Pack size	
Bronchospasm in patients with bronchial asthma or obstructive airways disease	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 4.9 Overdose Prescription only medicine Pack size	None proposed
Aggravation (worsening) of preexisting heart failure	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: Section 4.3 Contraindications Section 4.8 Undesirable effects Prescription only medicine Pack size	None proposed
Syncope	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: Section 4.8 Undesirable effects Prescription only medicine Pack size	None proposed
Decreased diabetic control, masking of hypoglycaemic effects	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: Section 4.4 Special warnings and precautions for use Section 4.5 Interactions with other medicinal products and other forms of interaction Section 4.6 Fertility, pregnancy and lactation Prescription only medicine Pack size	None proposed
Important Potential Risks		
Toxic skin reactions	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: Section 4.3 Contraindications Prescription only medicine	None proposed
Fibrosis conditions	Risk minimisation activities consist to	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
(Peyronie´s disease, retroperitoneal fibrosis, pulmonary fibrosis)	describe in relevant section of the SPC relevant information to minimise the risk: None proposed Prescription only medicine Pack size	
Interstitial lung disease / Interstitial pneumonitis	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: None proposed Prescription only medicine Pack size	None proposed
Fatal hepatotoxicity	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: None proposed Prescription only medicine Pack size	None proposed
Missing Information		
Children and adolescents under 18 years of age	Risk minimisation activities consist to describe in relevant section of the SPC relevant information to minimise the risk: Section 4.2 Posology and method of administration Prescription only medicine Pack size	None proposed

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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit risk assessment was considered positive. Therefore the RMS and CMS recommended approval of Bisoprolol Xantis 2.5 mg, 5 mg and 10 mg.