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Public Assessment Report

Scientific discussion

Furosemid Xantis 40 mg
furosemide

SH/H/0192/001/DC

Date: 03 December 2018

This module reflects the scientific discussion for the approval of Furosemide Xantis 40 mg. The procedure was finalised at 11 December 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 (SK, CZ) have granted a marketing authorisation for Furosemide Xantis 40 mg, tablets from XANTIS PHARMA LIMITED, Nicosia, Cyprus.

The product is indicated for
- *Oedema secondary to cardiac or hepatic disorders*
- *Oedema secondary to renal disorders (in nephrotic syndrome, treatment of the primary disease is essential)*
- *Oedema secondary to burn injury*
- *Arterial 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.

II. QUALITY ASPECTS

II.1 Introduction

Furosemid Xantis 40 mg tablets are white to off-white, round, biconvex tablets, half-scored on one side, diameter 7 mm.

Primary packaging: Blister PVC/PVdC/ALU

Secondary packaging: Paper folding box

Sizes of packaging: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 tablets

II.2 Drug Substance

INN: Furosemide

Molecular formula: $C_{12}H_{11}ClN_2O_5S$

Appearance: white or almost white, crystalline powder (Ph.Eur 9).

Solubility: practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides (Ph.Eur 9).

Manufacturing: The drug substance, furosemide, is manufactured by two suppliers IPCA LABORATORIES LIMITED, India and SRI KRISHNA PHARMACEUTICALS LIMITED, India. Both manufacturers have a valid CEP (IPCA: CEP R1-CEP 1998-020-Rev 06, SRI KRISHNA: CEP CEP R1-CEP 1999-137-Rev 06).
The control tests and specifications for drug substance product are adequately drawn up.

Stability: Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 5 years was justified.

Specification: The specification was established according to the monograph on Furosemide in Ph.Eur. The tests on residual solvents have been assessed by EDQM.

II.3 Medicinal Product

Pharmaceutical development: The aim of development was to formulate immediate release furosemide tablets. Production of tablets was tested by direct compression and wet granulation. Due to fact, that furosemide powder is very fine, electrostatically attracted to the sieve and equipment walls with poor flowability in excipients mixture, the wet (high shear) granulation has been chosen.

Justification for the choice of final dissolution conditions has been presented. The presented report describes the development of the dissolution method by using UV-VIS spectrophotometry.
The investigation of solubility of furosemide was performed at four pH values, i.e. at pH 1.2, 4.5, 5.8 and 6.8 at temperature 37 ± 0.5 °C. The solubility of furosemide is pH-dependent. Sink conditions were fulfilled in phosphate buffer pH 5.8 and pH 6.8.

The manufacturing process consists of following steps:
1. weighing of active pharmaceutical ingredient (API) and excipients
2. pre-granulation blending (lactose monohydrate, furosemide, hydroxypropylcellulose, low-substituted and starch pregelatinised)
3. preparation of granulation solution (purified water)
4. granulation in high shear mixer
5. sieving of wet granules
6. drying in fluid-bed dryer
7. sieving of dried granules
8. blending I (homogenisation) – dried granules and silica colloidal anhydrous
9. final blending (homogenisation)
10. compression

Specification: 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.

Stability: 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 **2 years** was considered acceptable.
Storage conditions *"Store in the original package in order to protect from light"* was accepted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There were no major objections with regard to quality part of the dossier during procedure. Applicant was asked to present data regarding the presence of only one polymorph (and testing method used), discriminatory power of dissolution method, functionality of breaking

line, stability testing in double PE bag in PP container, limit od dissolution, bulk packaging, declaration of conformity with respective guideline, limit for resistance to crushing. All issues have been adequately elucidated.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of furosemide are well known. As furosemide 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 was, thus, appropriate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Furosemid Xantis is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

The non-clinical data was based on literature overview of studies of pre-clinical pharmacology, pharmacokinetics and toxicology. This was considered adequate for a generic application.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted as a report 1 bioequivalence study.

IV.2 Pharmacokinetics

The study was an open label, two periods, two sequences, crossover, controlled, block randomized, bioequivalence study of Furosemid Xantis 40 mg tablet (test formulation) vs. equal dose of Lasix 40 mg tablets (reference formulation) in healthy, adult male and female volunteers with single dose administration under fasting conditions. Results are presented in **Table 1.**

Table 1: The mean values of furosemide pharmacokinetic parameters

Treatment = R

N = 32	Cmax (ng/ml)	AUC0-t (ng/ml*h)	AUC0-inf (ng/ml *h)	AUC%extra (%)	$T_{1/2}$ (hours)	MRT (hours)	N = 32	Tmax (hours)
Mean	1246.672	2931.900	2997.516	2.599	2.724	3.312	Median	1.375
SD	580.978	1059.898	1052.228	2.046	0.906	0.741	Min	0.500
CV	46.602	36.151	35.103	78.727	33.248	22.382	Max	4.000

Treatment=T

N = 32	Cmax (ng/ml)	AUC0-t (ng/ml*h)	AUC0-inf (ng/ml *h)	AUC%extra (%)	$T_{1/2}$ (hours)	MRT (hours)	N = 32	Tmax (hours)
Mean	1249.301	2948.582	3027.916	3.082	2.790	3.525	Median	1.375
SD	610.491	1182.925	1167.788	3.502	0.996	0.984	Min	0.750
CV	48.867	40.118	38.567	113.636	35.704	27.914	Max	4.000

The 90 % confidence intervals of the test/reference ratios were within the acceptance range (0.80–1.25) for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for furosemide. Significant period effect for AUC_{0-t} and significant subject (sequence) effect for C_{max} and AUC_{0-t} have been justified by the applicant and were thus acceptable.

Comparison of dissolution profiles in 0.1 M HCl, acetate buffer (pH=4.5), acetate buffer (pH=5.5) and phosphate buffer (pH=5.8) of Furosemid Xantis and Lasix have been submitted.

Table 7 Comparative dissolution profiles of products used in the bioequivalence study in phosphate buffer pH 5.8 as dissolution medium

Time (minutes)	Dissolved amount of furosemide (%, n = 12)			
	Lasix 40 mg, tablets BN 6JW1C - reference batch		Furosemid Xantis 40 mg, tablets BN 40190617 - clinical batch	
	Average	RSD	Average	RSD
5	56.6	17.2	65.2	2.9
10	75.4	12.7	83.8	1.6
15	83.7	9.4	91.0	1.2
20	88.2	7.2	94.5	1.1
30	92.7	4.9	97.5	0.9
45	94.7	3.5	98.7	0.8
60	95.4	2.8	99.0	0.8
Similarity factor *f2*	**59.6***			

*(calculated from 10, 15, 20, 30, 45 minutes)

Table 8 Comparative dissolution profiles of products used in the bioequivalence study in acetate buffer pH 5.5 as dissolution medium

Time (minutes)	Dissolved amount of furosemide (%, n = 12)			
	Lasix 40 mg, tablets BN 6JW1C - reference batch		Furosemid Xantis 40 mg, tablets BN 40190617 - clinical batch	
	Average	RSD	Average	RSD
5	65.6	5.1	64.4	3.0
10	84.0	3.9	83.5	2.1
15	90.9	3.3	90.9	1.8
20	93.5	3.2	94.6	1.5
30	95.5	3.0	97.7	1.3
45	96.4	3.1	99.1	1.1
60	96.7	3.0	99.5	1.1
Similarity factor *f2*	**similar (> 85 % in 15 minutes)**			

Table 9 Comparative dissolution profiles of products used in the bioequivalence study in acetate buffer pH 4.5 as dissolution medium

Time (minutes)	Dissolved amount of furosemide (%, n = 12)			
	Lasix 40 mg, tablets BN 6JW1C - reference batch		Furosemid Xantis 40 mg, tablets BN 40190617 - clinical batch	
	Average	RSD	Average	RSD
5	29.4	12.9	25.5	4.5
10	45.2	9.3	40.3	3.0
15	53.6	8.4	49.7	2.6
20	62.1	5.7	56.5	2.4
30	71.9	4.1	66.1	2.1
45	81.2	3.9	75.0	1.9
60	86.1	3.2	80.7	1.8
Similarity factor *f2*	**63.2***			

*(calculated from 10, 15, 20, 30, 45 minutes)

Table 10 Comparative dissolution profiles of products used in the bioequivalence study in 0.1 M hydrochloric acid with 2 % of SDS as dissolution medium

Time (minutes)	Dissolved amount of furosemide (%, n = 12)			
	Lasix 40 mg, tablets BN 6JW1C - reference batch		Furosemid Xantis 40 mg, tablets BN 40190617 - clinical batch	
	Average	RSD	Average	RSD
5	27.6	24.5	22.4	6.5
10	46.3	14.1	37.8	4.5
15	58.0	9.9	47.0	4.0
20	66.1	7.5	53.7	4.2
30	76.2	5.2	63.0	3.6
45	84.2	4.1	71.9	3.3
60	88.3	3.6	77.7	3.2
Similarity factor *f2*	**46.7***			

*(calculated from 10, 15, 20, 30, 45 minutes)

The bioequivalence between Furosemid Xantis 40 mg manufactured by Saneca Pharmaceuticals a.s. and Lasix 40 mg tablets, by Sanofi-Aventis Deutschland GmbH has been established.

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 Furosemid xantis 40 mg.

- Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Dehydratation • Severe electrolyte imbalance • Impaired renal function • Gout
Important potential risks	• Persistent ductus arteriosus in premature infants • Ototoxicity • Diabetes mellitus • Nephrocalcinosis/kidney stones in premature infants
Missing information	• Effects in children when ingested together with breast milk

IV.4 Discussion on the clinical aspects

No major objections have been identified with regard to clinical part of the dossier. There was one open issue concerning list of good clinical practice (GCP) inspections performed by EU authorities at study site on Days 70, 120 and 180. Eventually, applicant provided RMS with appropriate information on GCP inspection outcome. The bioequivalence between Furosemid Xantis 40 mg manufactured by Saneca Pharmaceuticals a.s. and Lasix 40 mg tablets, by Sanofi-Aventis Deutschland GmbH has been established in submitted bioequivalence study.

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 PL 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 overall benefit/risk of Furosemid Xantis 40 mg is positive.