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Public Assessment Report

Scientific discussion

Dutasterid/Tamsulozín Xantis
Dutasteride/tamsulosin hydrochloride

SK/H/0201/001/DC

Date: November 2019

This module reflects the scientific discussion for the approval of Dutasterid/Tamsulozín Xantis. The procedure was finalised at 29.07.2019. 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 Dutasterid/Tamsulozín Xantis, from *Xantis Pharma Limited, Cyprus.*
The product is indicated for Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).

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

Dutasterid/Tamsulozín Xantis are oblong, hard gelatin capsules of size 21.4 mm x 7.4 mm approximately with brown body and orange cap printed with C001 in black ink.
Each hard capsule contains tamsulosin hydrochloride modified release pellets and one dutasteride soft gelatin capsule.
Hard capsules are packed in HDPE bottle with silica gel desiccant contained in the cap.

II.2 Drug Substance

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Dutasterid/Tamsulozín Xantis are of sufficient quality in view of the present European regulatory requirements. Both drug substances, dutasteride and tamsulosin, are described in the Ph.Eur.

The control tests and specifications for drug substance product are adequately drawn up.
Stability studies have been performed with the drug substance. The proposed retest period of dutasteride as stated on the CEP is 2 years if stored in a double polyethylene bag in a triple laminated bag (Polyethylene terephtalate/aluminium foil/polyethylene) placed in a polyethylene container.
The re-test period of tamsulosin hydrochloride as stated on the CEP is 3 years if stored in a double polyethylene bag placed in a polyethylene drum.
The last update of the CEP for tamsulosin hydrochloride held by Zentiva K.S., CZ has been provided.

The drug substance specification fully complies with Ph.Eur.

II.3 Medicinal Product

The developed product is a hard capsule containing dutasteride and tamsulosin hydrochloride.
Dutasteride/Tamsulosin 0.5 mg/0.4 mg, capsules hard, are oblong hard gelatine capsules, Nº 0, body of brown colour and cap of orange colour with black code C001 on the cap. Each capsule contains:

- one oblong soft gelatine capsule of Dutasteride (approximately 16.5 x 6.5 mm) of light yellow colour, filled with transparent liquid
- approximately 183.8 mg of modified release tamsulosin pellets with white to off white colour

The capsules are packed in HDPE bottle with silica gel desiccant contained in the cap. Each hard gelatine capsule contains 0.07% and 0.06% of dutasterid and tamsulosin hydrochloride, respectively.

The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturer of the finished product is Laboratorios Leon Farma, SA from Spain.

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 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 is justified. Storage conditions : Store below 30 °C, the product should be used within 90 days after opening in HDPE bottle with PP closure with desiccant.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of dutasteride and tamsulosin are well known. As dutasteride and tamsulosine are widely used, well-known active substances, 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)

Since Dutasterid/Tamsulozín 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.
Applicant presented data to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected.
Applicant submitted several documents concerning properties of dutasteride and data on LogKow for both dutasteride and tamsulosin which have been previously published.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dutasteride-tamsulosin is a combination of two drugs: dutasteride, a dual 5 α-reductase inhibitor and tamsulosin hydrochloride, an antagonist of α_{1a} and α_{1d} adrenoreceptors. These drugs have complementary mechanisms of action that rapidly improve symptoms, urinary flow and reduce the risk of acute urinary retention and the need for BPH related surgery.
Dutasteride inhibits both type 1 and type 2, 5 alpha-reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for prostate growth and BPH development. Tamsulosin inhibits α_{1a} and α_{1d} adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the α_1-receptors in the prostate are of the α_{1a} subtype.

IV.2 Pharmacokinetics

To support the application, the applicant has submitted as report 3 pivotal bioequivalence studies:
- ZNV-P0-421 - Single Dose Crossover Comparative Bioavailability Study of Dutasteride/Tamsulosin 0.5 mg / 0.4 mg Capsules in Healthy Male Volunteers / Fasting State

- ZNV-P2-465 - Single Dose Crossover Comparative Bioavailability Study of Dutasteride/Tamsulosin 0.5 mg/0.4 mg Capsules in Healthy Male Volunteers / Fed State
- ZNV-P7-519 - Multiple Dose Crossover Comparative Bioavailability Study of Dutasteride/Tamsulosin 0.5 mg/0.4 mg Capsules in Healthy Male Volunteers / Fed State

Also, two pilot studies TMS-PBE-02-ZNV/13 and TMS-PBE-01-ZNV/13 (under fasting and fed conditions) have been conducted during the product optimization to select optimal prototype modified release formulation. In these pilot studies the optimized selected formulation (Test 3) has shown bioequivalence for tamsulosin with the reference products Omnic and Combodart. Documentation for these studies has been submitted as synopsis only.

The **study no. ZNV-P0-421** was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions. A 0.5/0.4 mg hard capsule of either the test product, dutasteride/ tamsulaosin manufactured by Laboratorios Leon Farma S.A or the reference product, Duodart by GlaxoSmithKline GmbH & Co. KG, (from the German market), was administered in each period with a wash out period of 21 days between the two administrations.
The study included 48 subjects of which all completed the study and were included in the statistical analysis of the parent compounds dutasteride and tamsulosin.
The primary variables for the assessment of bioequivalence were AUC_{0-72} and C_{max} for dutasteride and AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for tamsulosin.

Results:

Pharmacokinetic Parameters

Dutasteride

PARAMETER	TEST (n=48) [b]		REFERENCE (n=48) [b]	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	2504.7	(28.4)	2708.6	(29.1)
ln (C_{max})	7.7835	(3.9)	7.8631	(3.7)
T_{max} (hours) [a]	3.50	(1.67-10.00)	2.50	(1.03-5.50)
AUC_{0-72} (pg·h/mL)	48054.4	(43.0)	50998.6	(45.3)
ln (AUC_{0-72})	10.6749	(4.6)	10.7323	(4.5)
λ_Z ($hours^{-1}$)	0.0246	(24.9)	0.0231	(24.5)
T_{half} (hours)	29.24	(20.4)	31.18	(20.1)

[a] Median (range)
[b]; n=4 for λ_Z and T_{half}

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=48)	REFERENCE (n=48)		LOWER	UPPER
C_{max}	15.7	2400.7	2599.4	92.35	87.54	97.44
AUC_{0-72}	11.2	43256.6	45812.4	94.42	90.87	98.11

[a] units are pg/mL for C_{max} and pg·h/mL for AUC_{0-72}

Pharmacokinetic Parameters

Tamsulosin

PARAMETER	TEST (n=48)		REFERENCE (n=48)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	15280.7	(24.3)	14086.0	(24.2)
ln (C_{max})	9.6058	(2.5)	9.5252	(2.5)
T_{max} (hours) [a]	5.00	(2.50-7.00)	5.00	(2.50-7.03)
AUC_{0-T} (pg·h/mL)	201910.1	(36.7)	197262.8	(31.9)
ln (AUC_{0-T})	12.1560	(2.8)	12.1451	(2.5)
AUC_{0-12} (pg·h/mL)	102662.8	(27.6)	93714.7	(23.9)
AUC_{12-T} (pg·h/mL)	99247.3	(50.9)	103548.1	(45.6)
AUC_{0-24} (pg·h/mL)	151350.0	(30.2)	143319.3	(25.9)
$AUC_{0-\infty}$ (pg·h/mL)	205725.4	(38.5)	201260.1	(33.3)
ln ($AUC_{0-\infty}$)	12.1707	(2.9)	12.1616	(2.6)
$AUC_{0-24/\infty}$ (pg·h/mL)	75.41	(9.1)	73.01	(10.6)
Residual area (%)	1.45	(100.1)	1.63	(98.0)
λ_Z ($hours^{-1}$)	0.0638	(18.4)	0.0636	(21.9)
T_{half} (hours)	11.29	(21.8)	11.44	(23.3)

[a] Median (range)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS [a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=48)	REFERENCE (n=48)		LOWER	UPPER
C_{max}	13.9	14851.2	13701.1	108.39	103.39	113.64
AUC_{0-T}	14.5	190230.2	188168.7	101.10	96.21	106.23
$AUC_{0-\infty}$	14.6	193049.7	191304.2	100.91	96.01	106.07

[a] units are pg/mL for C_{max} and pg·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

The **study no. ZNV-P2-465** was an open-label, randomized, two-treatment, two-sequence, two-period,
two-way crossover, single-dose bioavailability study conducted under fed conditions. A 0.5/0.4 mg hard capsule of either the test product, dutasteride/ tamsulaosin manufactured by Laboratorios Leon Farma S.A or the reference product, Duodart by GlaxoSmithKline GmbH & Co. KG, (from the German market), was administered in each period with a wash out period of 21 days between the two administrations.
The study included 72 subjects of which 66 completed the study and were included in the statistical analysis of the parent compounds dutasteride and tamsulosin.
The primary variables for the assessment of bioequivalence were AUC_{0-72} and C_{max} for dutasteride and AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for tamsulosin.

Results:

Pharmacokinetic Parameters

Dutasteride

PARAMETER	TEST (n=66) [b]		REFERENCE (n=66) [b]	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	2118.7	(45.9)	2069.6	(45.1)
ln (C_{max})	7.5682	(5.6)	7.5309	(6.3)
T_{max} (hours) [a]	5.50	(2.00-24.05)	5.29	(2.00-24.00)
AUC_{0-72} (pg·h/mL)	46098.8	(50.2)	45511.5	(51. 2)
ln (AUC_{0-72})	10.6042	(5.2)	10.5851	(5.3)
λ_Z ($hours^{-1}$)	0.0294	(51.3)	0.0293	(24.8)
T_{half} (hours)	26.65	(26.6)	25.04	(23.8)

[a] Median (range)

[b] n=65 for $AUC_{0-72;}$ n=16 for $\lambda_{Z,}$ and T_{half}

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=66) [b]	REFERENCE (n=66) [b]		LOWER	UPPER
C_{max}	22.4	1939.0	1862.6	104.10	97.63	111.00
AUC_{0-72}	7.8	40353.4	39531.0	102.08	99.78	104.43

[a] units are pg/mL for C_{max} and pg·h/mL for AUC_{0-72}

[b] n= 65 for AUC_{0-72}

Pharmacokinetic Parameters

Tamsulosin

PARAMETER	TEST (n=66) [b]		REFERENCE (n=66) [b]	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (pg/mL)	10833.3	(32.9)	10367.5	(34.9)
ln (C_{max})	9.2338	(3.8)	9.1847	(3.9)
T_{max} (hours) [a]	7.50	(4.50-24.00)	8.00	(4.50-24.00)
AUC_{0-T} (ng·h/mL)	198254.1	(44.8)	202696.9	(46.4)
ln (AUC_{0-T})	12.1131	(3.4)	12.1361	(3.2)
AUC_{0-12} (pg·h/mL)	61706.1	(38.2)	64204.0	(38.8)
AUC_{12-T} (pg·h/mL)	136548.0	(62.4)	138492.8	(60.3)
AUC_{0-24} (pg·h/mL)	120870.3	(32.2)	123374.6	(36.0)
$AUC_{0-\infty}$ (pg·h/mL)	198079.6	(41.9)	204055.8	(44.6)
ln ($AUC_{0-\infty}$)	12.1237	(3.1)	12.1459	(3.2)
$AUC_{0-24/\infty}$ (pg·h/mL)	64.86	(13.9)	64.47	(13.8)
Residual area	2.16	(102.6)	2.28	(96.1)
λ_Z ($hours^{-1}$)	0.0616	(19.6)	0.0620	(21.5)
T_{half} (hours)	11.78	(23.7)	11.77	(24.6)

[a] Median (range)

[b] n= 65 for AUC_{0-T}, AUC_{0-12}, AUC_{12-T}, and AUC_{0-24} and n= 57 for $AUC_{0-\infty}$, $AUC_{0-24/\infty}$, residual area, λ_Z, and T_{half}

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS [a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=66)[b]	REFERENCE (n=66)[b]		LOWER	UPPER
C_{max}	20.6	10218.4	9732.6	104.99	98.96	111.39
AUC_{0-T}	16.4	182038.6	186425.1	97.65	93.10	102.42
$AUC_{0-\infty}$	16.0	183529.9	187986.4	97.63	92.89	102.62

[a] units are pg/mL for C_{max} and pg·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

[b] n= 65 for AUC_{0-T} and n= 57 for $AUC_{0-\infty}$

The **study no. ZNV-P7-519** was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, multiple-dose bioavailability study conducted under fed conditions. A 0.5/0.4 mg hard capsule of either the test product, dutasteride/ tamsulaosin manufactured by Laboratorios Leon Farma S.A or the reference product, Duodart by GlaxoSmithKline GmbH & Co. KG, (from the German market), was administered once daily for 7 consecutive days in each period with a wash out period of 21 days between the two periods.

The study included 72 subjects of which 62 completed the study and were included in the statistical analysis of the parent compound tamsulosin.

The primary variables for the assessment of bioequivalence were $AUC_{(0-\tau)}$, $C_{max,ss}$, and $C_{\tau,ss}$ for tamsulosin.

Results:

Pharmacokinetic Parameters

Tamsulosin

PARAMETER	TEST (n=62)		REFERENCE (n=62)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
$C_{max,ss}$ (pg/mL)	13219.8	(35.0)	12284.3	(36.1)
ln ($C_{max,ss}$)	9.4368	(3.4)	9.3558	(3.7)
$T_{max,ss}$ (hours)[a]	6.00	(3.00-12.00)	6.00	(3.00-24.00)
$AUC_{(0-\tau)}$ (pg·h/mL)	170491.1	(43.6)	161952.5	(40.9)
ln ($AUC_{(0-\tau)}$)	11.9709	(3.2)	11.9238	(3.1)
$C_{\tau,ss}$ (pg/mL)	4615.6	(64.6)	4594.2	(58.4)
ln ($C_{\tau,ss}$)	8.2732	(6.8)	8.2954	(6.3)
Fluctuation (%)	142.51	(36.4)	132.73	(32.0)
C_{pd-48} (pg/mL)	4081.5	(57.9)	4110.4	(53.6)
C_{pd-24} (pg/mL)	4501.8	(66.2)	4334.8	(54.7)
C_{pd0} (pg/mL)	4350.8	(61.4)	4310.1	(54.3)

[a] Median and range are presented

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS [a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=62)	REFERENCE (n=62)		LOWER	UPPER
$C_{max,ss}$	16.5	12529.2	11555.9	108.42	103.20	113.91
$AUC_{(0-\tau)}$	13.0	157855.6	150734.5	104.72	100.74	108.87
$C_{\tau,ss}$	22.4	3907.5	4003.8	97.60	91.31	104.31

[a] units are pg/mL for $C_{max,ss}$ and $C_{\tau,ss}$, and pg·h/mL for $AUC_{(0-\tau)}$

This medicinal product has following pharmaceutical form: it is a hard capsule containing one soft-gelatin capsule of dutasteride (immediate release) and pellets of tamsulosin (modified-release). Considering the fact that this medicinal product contains also pharmaceutical form that is modified-release, the type and number of bioequivalence studies submitted is acceptable. Also, considering the fact that only tamsulosin is in the modified-release form, it is acceptable that in multiple dose study only pharmacokinetics of tamsulosin is studied.

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 Dutasterid/Tamsulozín Xantis.

Safety specification

Summary of safety concerns proposed by the Applicant in RMP version 0.2.

Summary of safety concerns	
Important identified risks	**Risks associated with tamsulosin:** - Intraoperative Floppy Iris Syndrome
Important potential risks	**Risks associated with dutasteride:** - Male breast cancer - High-grade prostate cancer
Missing information	Use in patients with hepatic impairment

Pharmacovigilance Plan

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

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Intraoperative Floppy Iris Syndrome	Routine risk communication: *SmPC section 4.8.* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Prevention of the risk factors that may lead to intraoperative floppy iris syndrome included in SmPC sections 4.4* *How to prevent the risks of cataract (cloudy lens) surgery is included in PL sections 2* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	None
Male breast cancer	Routine risk communication: *SmPC section 4.8.* *PL section 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for monitoring of specific signs and syndrome of male breast cancer is included in SmPC sections 4.4* *How to detect early sign and symptoms of breast cancer is included in PL sections 2* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	None

High-grade prostate cancer	Routine risk communication: *SmPC section 5.1* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for monitoring of the PSA concentrations as test for prostate cancer is included in SmPC section 4.4* *How to detect early signs of high-grade prostate cancer is included in PL sections 2* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	None
Use in patients with hepatic impairment	Routine risk communication: *N/A* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for the use of medical product in patients with hepatic impairment is included in SmPC sections 4.2, 4.4* *Recommendation for patients who have severe problems with liver is included in PL section 2* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	None

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 Dutasterid/Tamsulozín Xantis.