COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tamsulosine HCl Krka 0.4 mg prolonged-release tablets

(tamsulosin hydrochloride)

NL/H/4379/001/DC

Date: 13 August 2019

This module reflects the scientific discussion for the approval of Tamsulosine HCl Krka 0.4 mg. The procedure was finalised on 3 June 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tamsulosine HCl Krka 0.4 mg prolonged-release tablets from Krka d.d.

The product is indicated for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Omnic Ocas 0.4, prolonged-release tablets 0.4 mg (NL licence RVG 30565, MRP NL/H/0554/001) which has been registered in the Netherlands by Astellas Pharma Europe B.V. since 2004. The first authorisation was granted in 1995 for Omnic 0.4 mg modified-release capsules (NL Licence RVG 17931).

The concerned member states (CMS) involved in this procedure were Belgium, France, Ireland and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Tamsulosine HCl Krka 0.4 mg is a white, unscored, round tablet, debossed on one side with "T9SL" and "0.4" on the other side. Each prolonged-release tablet contains 0.4 mg tamsulosin hydrochloride, corresponding with 0.367 mg tamsulosin.
The formulation involves a tablet in tablet concept wherein the active substance is in the outer core. The inner tablet is of the same composition as the outer tablet, with the addition of iron oxide.

The tablets are packed in OPA/Al/PVC-Al blister, PVC/PCTFE (Aclar)-Al blister, PVC/PVdC-Al blister or PVC/PE/PVdC-Al blister.

The used excipients are:
Inner core tablet – hypromellose (E464), microcrystalline cellulose (E460), carbomer, silica colloidal anhydrous (E551), iron oxide red (E172) and magnesium stearate (E470b)
Outer tablet - microcrystalline cellulose (E460), hypromellose (E464), carbomer, silica colloidal anhydrous (E551) and magnesium stearate (E470b).

II.2 Drug Substance

The active substance is tamsulosin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder. It is sparingly soluble in water and methanol, slightly soluble in glacial acetic acid and ethanol and practically insoluble in ether. Tamsulosin hydrochloride is not hygroscopic. The active substance does not exhibit polymorphism. It has one chiral centre, and it is manufactured as the R(-)-enantiomer.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the Ph. Eur. and the CEP, with additional requirements for particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches, one for each production site.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH's objective was to develop tamsulosin HCl prolonged-release tablets which are a generic form of the product Omnic Ocas 0.4, prolonged release tablets, film-coated with a different composition but with a similar dissolution profile and gelling behaviour.
The batch used for the bioequivalence trial displayed cracks in the outer mantle and was therefore not complying with the drug product specifications. Comparative dissolution profiles between batches without the cracks are similar to the biobatch with the cracks. It

has been demonstrated that the cracks do not affect the dissolution and the biobatch is considered acceptable in order to present the tamsulosin HCl modified release tablets.
Furthermore batch analytical data from batches with out of specification results for assay have been provided. Since the manufacturer demonstrated that no consistent product in line with the specification could be produced additional process development has been performed. As a result the composition of the batches slightly differs to that of the biobatch. However, the batch used in the bioequivalence study is considered to be representative for the batches to be marketed.

Manufacturing process
The manufacturing process consists of the preparation of the compression blend and compressing the inner core, followed by the preparation of the outer core compression blend and compressing it around the inner core. The product is manufactured using conventional manufacturing techniques. Process validation has been performed on three batches, of each site, of the maximum batch size. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, hardness, friability, water content, dissolution, identification, assay, uniformity of dosage units, impurities and microbial contamination. The release and shelf-life specifications are not identical, wider limits for hardness, water content, assay, and impurities are set for shelf-life. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on 15 production scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on four commercial scale batches. In addition stability data on 6 development batches have been provided. All batches were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in oPA/Al/PVC-Al blister, PVC/PE/PVDC-Al blister or PVC/PVDC-Al blister. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light.
Based on the included data the shelf-life that can be granted is 36 months when packed in any of the blister types, i.e. OPA/Al/PVC-Al blister, PVC/PCTFE (Aclar)-Al blister, PVC/PVdC-Al blister or PVC/PE/PVdC-Al blister.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. The excipient magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tamsulosine HCl Krka has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tamsulosine HCl Krka 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Omnic Ocas 0.4, prolonged-release tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tamsulosin hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Tamsulosine HCL Krka 0.4 mg prolonged-release tablets (Krka d.d., Slovenia) is compared with the pharmacokinetic profile of the reference product Omnic Ocas 0.4 mg prolonged release tablets (Astellas Pharma, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of the reference products in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods are adequately validated and considered acceptable for analysis of the plasma samples. The methods used in the bioequivalence studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Bioequivalence study 1 – single dose under fasted and fed conditions
Design
A single-dose, 4-period cross-over bioequivalence study was carried out under fasted and fed conditions in 36 healthy male volunteers, aged 19-54 years. Each subject received a single dose (0.4 mg) of one of the 2 tamsulosin formulations under fasting and fed conditions. For the fasting condition, the tablets were administered in solid form with 240 ml water after overnight fasting. Fasting was continued for 4 hours after dosing.
For the fed condition, after an overnight fast, the tablets were administered in solid form with 240 ml water, 30 minutes after the start of intake of a high fat, high caloric breakfast (240 ml whole milk, 2 eggs fried in butter, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with 11 g of butter, and 2 strips of bacon). The meal used in the study included 112 calories of protein, 240 calories of carbohydrate and 614 calories of fat for a total of 966 calories. The relative caloric content for each component corresponds to approximately 12%, 25% and 63% for protein, carbohydrate and fat, respectively. This is in accordance with the *guideline for the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr*).
For each subject there were 4 dosing periods, separated by a washout period of 7 days.

Blood samples were collected:
Fasted arm - pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.
Fed arm - pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours

Results

One subject was withdrawn before the start of period II, because of a positive drug test. Thirty-five subjects completed the study entirely, and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tamsulosin under fasted conditions.

Treatment N = 35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	139 ± 62	149 ± 67	7.2 ± 1.9	5.5 (2.0 – 8.0)	12.6 ± 3.6
Reference	134 ± 57	144 ± 60	6.7 ± 2.0	5.5 (3.0 – 16.0)	12.1 ± 3.1
***Ratio (90% CI)**	1.04 (0.97 – 1.11)	1.04 (0.97 – 1.11)	1.09 (1.01 – 1.16)	---	---
CV (%)	17.3	17.0	17.6	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tamsulosin under fed conditions.

Treatment N = 35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	178 ± 79	186 ± 81	9.6 ± 3.0	5.5 (3.0 – 12.0)	12.3 ± 4.0
Reference	184 ± 80	193 ± 85	10.9 ± 4.1	7.0 (3.0 – 16.0)	11.4 ± 2.7
***Ratio (90% CI)**	0.95 (0.89 – 1.01)	0.94 (0.89 – 1.01)	0.90 (0.83 – 0.98)	---	---
CV (%)	16.2	15.7	21.5	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of tamsulosin under fasted and fed conditions, it can be concluded that Tamsulosine HCL Krka 0.4 mg prolonged-release tablets and the Omnic Ocas 0.4 mg prolonged-release tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study 2 – multiple dose under fasted conditions

Design

A multiple-dose, 2-way cross-over bioequivalence study was carried out under fasted conditions in 36 healthy male volunteers, aged 28-55 years. Each subject received a single dose (0.4 mg) of one of the 2 tamsulosin formulations once daily for 7 days, under fasting conditions. At all days, the tablets were administered at the facility. At day 7, the tablets were administered in solid form with 240 ml water after overnight fasting. Fasting was continued for 4.5 hours after dosing.

For each subject there were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose at -48, -24h and 0h and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16 and 24 hours after administration of the products.

The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

One subject withdrew for personal reasons before dosing in period II. Thirty-five subjects completed the study entirely, and were included in the analysis.

Pre-dose concentrations at times -48, -24 and 0 hours demonstrated no significant difference between trough levels (p-value = 0.339) and interactions between the treatment received and through levels were also found to be not statistically significant (p-value = 0.320). Based on these two statistical tests, steady-state was considered to have been achieved.

Table 3. The steady state pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of tamsulosin under fasted conditions.

Treatment N = 35	**AUC_{τ}** ng.h/ml	**C_{-48h}** ng/ml	**C_{-24h}** ng/ml	**C_{0h}** ng/ml	**$C_{max,ss}$** ng/ml	**$C_{min,ss}$** ng/ml	**t_{max}** h	**Fluctuation** %
Test	135 ± 60	2.96 ± 1.81	2.89 ± 1.83	2.89 ± 1.89	9.4 ± 3.3	2.8 ± 1.9	5.0 (2.0 – 6.5)	128 ± 39
Reference	134 ± 51	3.40 ± 1.83	2.98 ± 1.89	3.11 ± 1.95	8.9 ± 2.9	2.9 ± 1.7	5.0 (3.0 – 16.0)	115 ± 36
***Ratio (90% CI)**	0.99 (0.91 –	---	---	---	1.06 (0.98 –	1.00 (0.85 –	---	---

	1.08)				1.15)	1.17)		
CV (%)	21	---	---	---	20.6	41.7	---	---

AUC_τ area under the plasma concentration-time curve over the dosing interval
$C_{max,ss}$ maximum plasma concentration steady state
$C_{min,ss}$ minimum plasma concentration steady state
t_{max} time for maximum concentration

**ln-transformed values*

The 90% confidence intervals calculated for AUC_τ, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of tamsulosin under fasted conditions, it can be concluded that Tamsulosine HCL Krka 0.4 mg prolonged-release tablets and Omnic Ocas 0.4 mg prolonged-release tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements for products with proplonged release characteristics outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Tamsulosine HCL Krka.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	• Orthostatic hypotension • Intraoperative Floppy Iris Syndrome • Angioedema
Important potential risks	• Concomitant administration with strong CYP3A4 inhibitors
Missing information	• Administration in paediatric patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Omnic Ocas. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management

is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Tanyz prolonged-release hard capsules 0.4 mg (parent PL). The parent PL was approved in the MR Renewal Procedure FI/H/494/001/R/001. The bridging report has been found acceptable. Bridging is adequately justified for design and layout as well as for content.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tamsulosine HCL Krka 0.4 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and is a generic form of Omnic Ocas 0.4 mg, prolonged-release tablets. Omnic 0.4 mg is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents, under fasting and fed conditions and at steady state.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tamsulosine HCL Krka 0.4 mg prolonged-release tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 June 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse