

Public Assessment Report

Scientific discussion

**Tamsulosine HCl Zentiva 0.4 mg,
prolonged-release tablets**

(tamsulosin hydrochloride)

NL/H/3282/001/MR

Date: 25 March 2015

This module reflects the scientific discussion for the approval of Tamsulosine HCl Zentiva 0.4 mg, prolonged-release tablets. The procedure was finalised at 19 February 2015. 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 Tamsulosine HCl Zentiva 0.4 mg, prolonged-release tablets, from Zentiva a.s.

The product is indicated for the treatment of 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 mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Omnic Ocas 0.4, prolonged release tablets 0.4 mg (NL license RVG 30565) which has been registered in the Netherlands by Astellas Pharma Europe B.V. since 2004 (original product). The first authorisation was granted in 1995 for Omnic 0.4 mg modified release capsules (RVG 17931).

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, France, Greece, Hungary, Latvia, Lithuania, Poland and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

The drug product is a white, un-scored, round tablet with a diameter of 9 mm, debossed on one side with "T9SL" and "0.4" on the other side, and contains as active substance 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 PVC/PVDC/Al, PVC/Aclar/Al or oPA/Al/PVC/Al blister packs.

The used excipients are:

Inner core tablet: hypromellose, microcrystalline cellulose, carbomer, silica colloidal anhydrous, iron oxide red and magnesium stearate.

Outer tablet: microcrystalline cellulose, hypromellose, carbomer, silica colloidal anhydrous, and magnesium stearate.

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 sparingly soluble in water and slightly soluble in acetone, ethanol, ethyl acetate and methanol. Tamsulosin hydrochloride is not hygroscopic. It has one centre of optical activity, 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 European Pharmacopoeia.

Manufacturing process

The manufacturing process of (R)-tamsulosin hydrochloride consists of two steps. The used solvents have been described. The drug substance has been adequately characterized and acceptable specifications have been adopted for the solvents and reagents.

Quality control of the drug substance

The specification of the drug substance is described in the CEP and is considered to be acceptable. The methods have been adequately validated. Batch analytical data from the two manufacturing sites used have been included and are in compliance with the proposed specification.

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 consist 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. Process validation has been performed on three pilot scaled batches demonstrating compliance with the specification.

Control of excipients

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

Quality control of the drug product

The product specification includes tests for appearance, hardness, friability, water content, dissolution, identification by HPLC and TLC, assay, uniformity of dosage units, impurities and microbial contamination. The release and shelf-life specification differ for hardness, water content and impurities.

The analytical methods have been adequately described and validated. Batch analytical data on six production scaled batches, three per manufacturing site, have been included. Three batches were produced without the aforementioned corrections and thus demonstrated cracks on the side. Besides appearance all batches complied with the specification.

Stability of drug product

The MAH included stability data on batches stored in four different types of packaging (oPA/Al/PVC/Al, PVC/PVDC/Al, PVC/PCTFE (Aclar)-Al, and PVC/PE/PVDC/Al). Ten batches were stored for 6 months at accelerated conditions and 24 or 36 months at long term conditions. No changes or out of specification results were observed.

A photostability study has been performed and no change was observed between the dark blistered control and the exposed tablets. However exposed bulk tablets demonstrated an increase in impurities.

Based on the included data the shelf-life that can be granted is 36 months packed in OPA/Al/PVC-Al blister, PVC/PCTFE (Aclar)-Al blister or PVC/PVDC-Al blister with the storage condition store in the original package in order to protect from light. The PVC/PE/PVDC-Al blister was not granted.

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

No materials from human and/or animal origin are contained or used in the manufacturing process of the medicinal product. 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 Zentiva 0.4 mg, prolonged-release tablets have 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 Zentiva 0.4 mg, prolonged-release tablets are 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 which is available on the European market. Reference is made to the preclinical data obtained with the innovator product Omnic Ocas 0.4, prolonged release tablets, film-coated. 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 Zentiva 0.4 mg prolonged-release tablets (Zentiva a.s., Czech Republic) 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 study 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.

Bioequivalence study 1 – single dose under fasted and fed conditions

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

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 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-∞} 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-∞} 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 | | | | | |

**In-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-∞} 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% | 0.95 | 0.94 | 0.90 | --- | --- |

| | | | | | |
|---|---------------|---------------|---------------|-----|-----|
| CI) | (0.89 – 1.01) | (0.89 – 1.01) | (0.83 – 0.98) | | |
| CV (%) | 16.2 | 15.7 | 21.5 | --- | --- |
| AUC_{0-∞} 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 | | | | | |

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Zentiva 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

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 – 1.08) | --- | --- | --- | 1.06 (0.98 – 1.15) | 1.00 (0.85 – 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 | | | | | | | | |

**In-transformed values*

The 90% confidence intervals calculated for AUC_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 conditions, it can be concluded that Tamsulosine HCL Zentiva 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 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 Zentiva 0.4 mg prolonged-release tablets.

- Summary table of safety concerns as approved in RMP

| | |
|----------------------------|--|
| Important identified risks | <ul style="list-style-type: none"> - Allergic reactions to the drug including skin rash (which can be itchy), hives, swelling of eyelids, face, lips, arms or legs - Stevens-Johnson syndrome - Orthostatic hypertenstion - Intraoperative floppy iris syndrome (IFIS) |
| Important potential risks | <ul style="list-style-type: none"> - Cardiovascular events (other than cardiac failure), including atrial fibrillation, tachycardia and arrhythmias associated with tamsulosin - Depression |
| Missing information | <ul style="list-style-type: none"> - Use in patients with severe renal impairment - Use in children younger than 18 years - Use in pregnancy and lactation |

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 0.4 mg, prolonged-release tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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 Protam 0.4 mg prolonged-release tablets (NL/H/1886/001). The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tamsulosine HCL Zentiva 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.

The Board followed the advice of the assessors. The marketing authorisation was granted in the Netherlands on 26 May 2014.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tamsulosine HCL Zentiva 0.4 mg prolonged-release tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 19 February 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|-------|------------------|----------------------|--------------------------------|------------------------------|------------------------|----------------------------|
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