CBG MEB

Public Assessment Report

Scientific discussion

Duktam 0.4 mg, modified release capsules

(tamsolusin hydrochloride)

NL/H/3570/001/MR

Date: 10 March 2017

This module reflects the scientific discussion for the approval of Duktam 0.4 mg, modified release capsules. The procedure was finalised on 28 September 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
EDQM	European Directorate for the Quality of Medicines
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 Duktam 0.4 mg, modified release capsules from Duke BV.

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 mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Omnic Ocas 0.4 mg, prolonged release tablets (NL License RVG 30565) which has been registered in Netherlands by Astellas Pharma Europe B.V. since 24 August 2004.

The concerned member state (CMS) involved in this procedure was Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Duktam is an orange/olive-green hard modified-release capsule, containing white to off-white pellets.

Each capsule contains as active ingredient tamsulosin hydrochloride 0.4 mg.

The capsules are packed in PVC/PE/PVDC/Aluminium blister packs and HDPE containers with PP child-resistant closures.

The excipients are:
Capsule content - microcrystalline cellulose, methacrylic acid-ethyl acrylate copolymer, polysorbate 80, sodium laurilsulfate, triethyl citrate and talc.
Capsule body – gelatin, indigotine (E 132), titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E 172) and black iron oxide (E 172).

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 which is slightly soluble in water, freely soluble in formic acid, slightly soluble in anhydrous ethanol.

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP with an additional limit for particle size. Batch

analytical data demonstrating compliance with this specification have been provided for eight commercial scale batches.

Stability of drug substance
The active substance is stable for five 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Initially the pellets had a different composition. Due to commercial reasons the composition was changed. This change in composition was supported by three bioequivalence studies with the current product versus the reference product Omnic Ocas, and additional dissolution studies, in accordance with the Guideline on the Investigation of Bioequivalence.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of weighing, preparation of the pellets (wet granulate, extrusion and drying), coating of the pellets, and filling the pellets into the capsules, followed by packaging. Adequate in-process controls to monitor the process have been set. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches.

Control of excipients
The excipients comply with the Ph.Eur. For the capsule shells separate in-house specifications are set. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, uniformity of mass, average mass, loss on drying, disintegration, dissolution, assay, uniformity of dosage units, impurities, microbiological quality and the identification of the colourants. With the exception of the parameter loss on drying the release and shelf-life requirements/limits are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from each of the two proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
For the product packed in the PVC/PE/PVDC-Al blister stability data has been provided for three full scale batches. Stability data of 36 months storage at 25ºC/60% RH and six months storage at 40ºC/75% RH have been provided. Under both long term and accelerated conditions values remain below the end of shelf-life limits.
For the product packed in the HDPE container stability data has been provided for three batches which have been stored 24 months at 25ºC/60% RH and six months at 40ºC/75% RH. The batches remain stable throughout the test period. No specific up or downward trends are observed.

On the basis of the available stability data the claimed shelf-life of three years, without specific storage conditions, can be granted.

The data of an adequate in-use study have been provided. No significant changes are observed compared to the initial results. A photostability study was also performed. The capsules were found to be photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided for gelatin and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Duktam 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 Duktam 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 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 initially submitted the results of three bioequivalence studies. A change in the manufacturing process was supported with the submission of a fourth bioequivalence study. A subsequent change in the composition of the modified release capsule, led to the submission of three pivotal bioequivalence studies. The latter three studies will be discussed below.

IV.2 Pharmacokinetics

Pivotal bioequivalence studies
The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Duktam 0.4 mg, modified release tablets (Duke BV, the Netherlands) is compared with the pharmacokinetic profile of the reference product Omnic Ocas 0.4 mg, modified release capsule (Astellas Pharma Europe, NL). A bioequivalence study was performed with healthy volunteers in fasting conditions, in postprandial conditions and after multiple dosing to achieve steady state plasma concentrations:

The choice of the reference product
The choice of the reference product in the three bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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

Bioequivalence study I – Duktam 0.4 mg, modified release capsule vs Omnic Ocas 0.4 mg, modified release capsule under fasting conditions
Design
An open label, single-dose, randomised, two-period, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 20-60 years. Each subject received a single dose (0.4 mg) of one of the two tamsulosin formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected 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.

The design of the study is acceptable.

Results
One subject was withdrawn after dosing in period II due to protocol violation and one subject withdrew for personal reasons. Therefore, 22 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=22	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	224 ± 96	235 ± 103	14.9 ± 4.8	5.0 (3.0 – 8.0)	13.3 ± 5.3
Reference	225 ± 116	237 ± 132	15.2 ± 5.2	5.5 (3.5 – 8.0)	13.0 ± 5.0
***Ratio (90% CI)**	1.02 (0.94 – 1.10)	1.02 (0.94 – 1.10)	0.98 (0.88 – 1.09)	--	--
CV (%)	14.7	14.8	20.3	--	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Bioequivalence study II – Duktam 0.4 mg, modified release capsule vs Omnic Ocas 0.4 mg, modified release capsule under fed conditions
Design
An open label, single-dose, randomised, two-period, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 20-62 years. Each subject received a single dose (0.4 mg) of one of the two tamsulosin formulations. The tablet was orally administered with 240 ml water 30 minutes after the intake of a standardised, high fat, high caloric-breakfast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected 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.

The design of the study is acceptable.

Results
One subject dropped out because he did not complete the intake of the breakfast. Therefore, 23 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=23	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	206 ± 74	216 ± 77	10.6 ± 2.9	10.0 (4.0 – 13.0)	12.7 ± 3.6
Reference	210 ± 73	220 ± 77	10.2 ± 2.9	9.0 (5.0 – 16.0)	13.2 ± 3.9
***Ratio (90% CI)**	0.98 (0.93 – 1.04)	0.99 (0.93 – 1.05)	1.05 (0.96 – 1.15)	--	--
CV (%)	11.8	11.3	18.5	--	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Bioequivalence study III – Duktam 0.4 mg, modified release capsule vs Omnic Ocas 0.4 mg, modified release capsule under fed conditions
Design
An open label, multiple-dose, randomised, two-period, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 21-59 years. Each subject received a single dose (0.4 mg) of one of the two tamsulosin formulations daily for six days. At day 1-5, the capsules were administered 30 min after start of intake of a light breakfast. At day six, the capsules were administered 30 min after start of intake of a standardised, high fat, high caloric breakfast, in solid form with 240 ml water. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose at day 4 and 5 and at day 6 pre-dose and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 14, 16 and 24 hours after administration of the products.

The design of the study is acceptable. The multiple dose, crossover study to assess bioequivalence is considered adequate.

Results
All 24 subjects completed the study were eligible for pharmacokinetic analysis.

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

Treatment N=23	AUC_{0-t} ng.h/ml	C_{max} ng/ml	C_{min} ng/ml	t_{max} h
Test	211 ± 88	13.3 ± 4.3	8.1 ± 3.8	9.0 (4.5 – 24.1)
Reference	229 ± 108	14.2 ± 6.1	8.0 ± 4.4	8.0 (4.0 – 24.2)
***Ratio (90% CI)**	0.94 (0.87 – 1.01)	0.97 (0.88 – 1.07)	1.05 (0.95 – 1.15)	--

CV (%)	14.6	19.3	19.1	--

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and C_{min} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Duktam is considered bioequivalent with Omnic Ocas.

The MEB has been assured that the bioequivalence studies has 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 Duktam.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Cardiac disorders • Ejaculation disorder and priapism • Intraoperative floppy iris syndrome (IFIS) • Orthostatic hypotension (dizziness, syncope and weakness) • Use in patients with severe hepatic impairment • Skin and subcutaneous disorders (angio-oedema, pruritus, rash, Stevens-Johnson syndrome and Urticaria)
Important potential risks	• Allergic reactions in patients with a past history of sulphonamide allergy • Depression • Drug interaction (alpha1-adrenoreceptor blockers, cimetidine, diclofenac, furosemide or warfarin) • Eye-disorders (other than IFIS) • Hyperglycaemia in patients with type 2 diabetes • Rhabdomyolysis
Missing information	• Use in children younger than 18 years • Use in patient with severe renal impairment

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

The package leaflet (PL) 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 test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Duktam 0.4 mg, modified release capsules has a proven chemical-pharmaceutical quality and is a generic form of Omnic Ocas 0.4 mg, prolonged release tablets. Omnic Ocas 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. Duktam was authorised on 6 February 2015

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Duktam with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 28 September 2016.

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