CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Tamsulosine HCl ratiopharm 0.4 mg prolonged release tablets
Ratiopharm Nederland B.V., the Netherlands

tamsulosin (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1887/001/DC
Registration number in the Netherlands: RVG 106172

24 March 2011

Pharmacotherapeutic group:	alpha-adrenoreceptor antagonists
ATC code:	G04CA02
Route of administration:	oral
Therapeutic indication:	lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).
Prescription status:	prescription only
Date of authorisation in NL:	15 February 2011
Concerned Member States:	Decentralised procedure with AT, BG, DE, ES, FR, HU, NO, and SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Tamsulosine HCl ratiopharm 0.4 mg prolonged release tablets, from Ratiopharm Nederland B.V. The date of authorisation was on 15 February 2011 in the Netherlands. The product is indicated for 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 SPC.

Tamsulosin binds selectively and competitively to the postsynaptic α1-adrenoceptors, in particular to subtypes α_{1A} and α_{1D}. Tamsulosin increases the maximum urinary flow rate. It relieves obstruction by relaxing smooth muscle in prostate and urethra thereby improving voiding symptoms. It also improves the storage symptoms in which bladder instability plays an important role. These effects on storage and voiding symptoms are maintained during longterm therapy. Observational data indicate that use of tamsulosin may lead to a delay in the need for surgery or catheterization. α1-adrenoceptor antagonists can reduce blood pressure by lowering peripheral resistance. No reduction in blood pressure of any clinical significance was observed during studies with tamsulosin.

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 license RVG 30565) which has been registered in the Netherlands by astellas Pharma Europe B.V. since 1995 (original product). In addition, reference is made to Omnic Ocas authorisations in the individual member states (reference product).
For Member State AT, reference is made to European Reference product Omnic Ocas 0,4, tabletten met verlengde afgifte 0,4 mg (NL license RVG 30565), marketed by Astellas Pharma Europe B.V.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies (1 single dose under fasted and fed conditions; 1 multiple dose under fasted conditions) in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Omnic Ocas 0.4 mg prolonged release tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is tamsulosin hydrochloride. The drug substance is described in the 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.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
The manufacturing process of (R)-tamsulosin hydrochloride 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 consists of in-house methods and is considered to be acceptable. The methods have been adequately validated. Batch analytical data from all three manufacturing sites have been included and are in compliance with the proposed specification.

Stability of drug substance
Stability data on the active substance have been provided for four full scaled batches stored at 25°C/60%RH (36 months) and 40°C/75%RH (6 months). The batches were adequately stored. All parameters tested are considered to be stable, no up or downward trends are observed in any of the examined parameters at long term, accelerated and in the photostability study. Based on the provided data a re-test period of 36 months can be granted for the product when stored under the proposed conditions.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU*.

Medicinal Product

Composition
The drug product is white, un-scored, round tablet with a 9 mm diameter, debossed on one side with "*T9SL*"and "*0.4*"on the other side. It is manufactured in the 0.4 mg strength. The used excipients are:
Inner core tablet - hypromellose, microcrystalline cellulose, carbomer, silica colloidal anhydrous, iron oxide red (E172), magnesium stearate.
Outer core - microcrystalline cellulose, hypromellose, carbomer, silica colloidal anhydrous, magnesium stearate.
The tablets are packed in blister packs. The excipients and packaging are usual for this type of dosage form.

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 a similar dissolution profile and gelling behaviour.

The formulation developed involves a tablet in tablet concept wherein the active substance is in the outer core. The inner tablet is of the same composition with addition of iron oxide as the outer tablet. The batch used for the bioequivalence trial displayed cracks in the outer mantle and was therefore not in line with the drug product specifications. Additional process development has been performed resulting in a more consistent product. As result the composition of the to be marketed batches slightly changed compared 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.

The MAH has committed to provide validation and release data from one specific site when the data are available.

Exipients

The excipients comply with the Ph.Eur. This is considered to be 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.

Microbiological attributes

The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth.

The tablets need to comply with Ph.Eur. 5.1.4, according to the acceptance criteria for microbial quality of non-sterile dosage forms (Table 5.1.4.-1 of Ph.Eur. 5.1.4). The harmonized method B is adopted for non-aqueous preparations for oral use. This is considered to be acceptable.

Stability tests on the finished product

The MAH included 10 batches stored in four different packagings (Al-Al blister, PVC/PCTFE-Al blister, PVC/PVdC-Al blister and PVC/PE/PVdC-Al blister) in the stability study. The 6 batches were stored for 6 months at accelerated conditions and 18 or 12 months at long term conditions. No changes or out of specification results were observed.

The batches packed in the PVC/PE/PVdC-Al blister were stored for 1 month at accelerated conditions and 0 months long term.

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 24 months packed in Al-Al blister, PVC/PCTFE 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.2 Non clinical aspects

This product is a generic formulation of Omnic Ocas, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of tamsulosin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Tamsulosin is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Tamsulosine HCl ratiopharm 0.4 mg prolonged release tablets (Ratiopharm Nederland B.V., the Netherlands) 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 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 - predose 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 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 ratiopharm 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 hrs after dosing.
For each subject there were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at -48 and -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_T** 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_{0-t} area under the plasma concentration-time curve from time zero to t hours
$C_{max,ss}$ 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_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 ratiopharm 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.

Risk management plan
Tamsulosin was first approved in1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of tamsulosin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is

based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The text is in line with the last approved version of the SPC of the reference product Omnic Ocas 0.4 mg prolonged release tablets (NL/H/0554/001), with the following amendments:

- Section 5.1 "*The need for surgery or catheterisation is significantly delayed.*" has been replaced by "*Observational data indicate that <> may lead to a delay in the need for surgery or catheterisation*".
- Sections 4.2 and 5.1: Implementation of the recently ended pediatric worksharing procedure of tamsulosine hydrochloride (NL-W-0014-pdWS-001) has been performed.

Readability test
The MAH submitted a readability test for the package leaflet of '*Tamsulosin HCl modified-release capsules*' (parent PL), together with a bridging report for the proposed package leaflet of '*Tamsulosin HCl prolonged release tablets*' (daughter PL).

Submission of a bridging report is only acceptable if the user consultation for the parent PL has been submitted in another application and the parent leaflet is approved prior to the approval of the daughter PL (see document on "*Consultation with target patient groups*"). The MAH stated that the user test has not been assessed previously, but has been submitted with renewal applications for Tamsulosin HCl modified-release capsules (NL/H/1620-1621/001/R/001). In this exceptional case, both the user test for the parent PL and the bridging report for the daughter PL have been assessed. Conclusions of both assessments are given below.

Readability test of PL of '*Tamsulosin HCl modified-release capsules' (parent PL)*:
Prior to testing, the PL has been reviewed by an experienced test administrator and revised by the MAH after problem areas were reported. A pilot round of testing (2 respondents) was performed, but no suggestions for changes were given based on this preliminary testing. Hence, the package leaflet has been tested in two rounds of 10 respondents. A questionnaire of 17 questions was used: 14 questions specific to the medicinal product were drawn up, sufficiently addressing the key safety messages, and 3 additional questions addressing the user friendliness of the PL. General and applicability questions were used to investigate the technical readability, comprehensibility of the text, traceability of the information and the applicability.
For 5 out of 14 questions in the first round and 3 out of 14 in the second round, at least 20% of participants scored '*moderate*' in locating the correct information, but no participant scored '*difficult*'. For 2 out of 14 questions in both rounds, 20% scored '*moderate*' in understanding the information, but no participant scored '*difficult*'. Because only '*difficult*' was interpreted as a negative result, no revisions were made during testing. For all questions, all participants were able to find the correct information and were able to answer each question correctly.
The results of the test indicate that the PL is well structured and organised, and written in a comprehensible manner. Based upon evaluation and analysis to be presented in the report, the package leaflet meets the necessary guidance for readability testing as outlined by European Council and MHRA guidance.

Bridging Report
The bridging report submitted by the MAH presents the differences between the user-tested PL of Tamsulosin HCl modified-release capsules (parent PL) and the PL of Tamsulosin HCl prolonged release tablets (daughter PL).
Content
The bridging report presents a side by side comparison of the leaflet text for the parent and daughter PLs. The textual differences are highlighted and at the end of the section, the impact on the results of the user testing is discussed where applicable. Although there are small differences in content between parent and daughter PL, most of them caused by differences in SPC's of both products, the differences are not considered to negatively influence the readability of the PL.

Overall, the leaflet content of parent and daughter PL is considered to be sufficiently similar to allow bridging.

Layout and style
The mock-ups of the user-tested parent leaflet and daughter leaflet are provided in the bridging report. The bridging report states that:
– no changes were made to the general design and lay out between the mother and daughter leaflet
– the font type, font size and use of colours (if any), headings and sub-headings is the same for both leaflets.

Conclusion
Bridging between the PL of Tamsulosin HCl modified-release capsules (parent PL) and the PL of Tamsulosin HCl prolonged release tablets (daughter PL) is acceptable, considering that the same layout and style is applied to the daughter PL mock-up as has been applied for the parent PL mock-up in the user test.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tamsulosine HCl ratiopharm 0.4 mg prolonged release tablets have a proven chemical-pharmaceutical quality and are a generic form of Omnic Ocas 0,4, prolonged release tablets 0.4 mg. 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 for products with proplonged release characteristics.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tamsulosine HCl ratiopharm 0.4 mg prolonged release tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 November 2010. Tamsulosine HCl ratiopharm 0.4 mg prolonged release tablets is authorised in the Netherlands on 15 February 2011.

A European harmonised birth date has been allocated 2 July 1993 and subsequently the first data lock point for tamsulosin is July 2011. The first PSUR will cover the period from approval to July 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be 31 March 2015.

The following post-approval commitments have been made during the procedure:

Quality - general
- The MAH has committed to continue all stability studies studies; long term up to 36 months, intermediate up to 12 months and accelerated up to 6 months.

Quality - medicinal product
- The MAH has committed to provide validation and release data from one specific site when the data are available.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
BPH	Benign Prostatic Hyperplasia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
LUTS	Lower Urinary Tract Symptoms
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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