CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Tamsulosine HCL retard 0.4 mg, modified-release capsules Stichting Registratiebeheer, the Netherlands

Tamsulosin 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/789/01/DC
Registration number in the Netherlands: RVG 33747

27 May 2009

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:	8 May 2008
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IT, LT, LV, NO, PT, SI, SK, UK
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 retard 0,4 mg modified-release capsules from Stichting Registratiebeheer. The date of authorisation was on 8 May 2008 in the Netherlands. 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 SPC.

The active compound in Tamsulosine retard capsule is tamsulosin hydrochloride. Tamsulosin binds selectively and competitively to postsynaptic α_{1A} adrenoreceptors, which convey smooth muscle contraction, thereby relaxing prostatic and urethral smooth muscle. Tamsulosin increases the maximum urinary flow rate by relaxing prostatic and urethral smooth muscle, thus relieving obstruction. Tamsulosin also improves the irritative and obstructive symptoms in which the contraction of smooth muscle in the lower urinary tract plays an important role. The medicinal product's effect on storage and voiding symptoms are maintained during long-term therapy, as a result of which the need for surgical treatment is significantly postponed.
Alpha-blockers in general can reduce blood pressure by lowering peripheral resistance. However, no reduction in blood pressure of any clinical significance was observed during studies with tamsulosin in normotensive patients.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Omnic 0.4 mg modified-release capsules (NL RVG 17931) which has been registered in the Netherlands by Astellas Pharma Europe B.V since 1995 (original product). In addition, reference is made to Omnic authorisations in the individual member states (reference product). For the CMS LT, LU and PT reference is made to the European Reference product (= original product mentioned earlier). Additional information regarding the European Reference Product according to the guidance given by the CMD(h) has been sent to all CMS with the RMS validation letter.

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 three bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product ALNA® 0.4 mg Retardkapseln modified release capsules, registered in Germany. ALNA is the German name of the reference product. 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.

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, an established active substance described in supplement 5.7 of the European Pharmacopoeia (Ph.Eur.*). Tamsulosin hydrochloride is a white or almost white powder. It is slightly soluble in water, sparingly soluble in ethanol and methanol and insoluble in non-polar organic solvents (hexane). Tamsulosin hydrochloride is a chiral substance with an optical rotation of -3.0° to -4.5° on anhydrous base. No polymorphs are known. The active substance is the R-isomer. The S-isomer is considered as an impurity. It originates from starting material SMA, which is also a chiral molecule.

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 substance is prepared by condensation of two starting materials. The possibility of occurrence of impurities arising from these starting materials has sufficiently been discussed by the DMF-holder. Reprocessing takes place if one of the intermediates does not comply with its specification. Adequate specifications are applied for the intermediates.

Specification
The control tests and specifications for drug substance product are adequately drawn up in view of the Ph.Eur. monograph and the characteristics of the finished product. Batch analytical data demonstrating compliance with this specification have been provided for 3 production scaled batches.

Stability
Stability studies have been performed with the drug substance at long term and accelerated conditions. No significant changes in any parameters were observed. The proposed retest period of 24 months is justified. The substance should be stored in the original packaging for protection from light.

Two post-approval commitments regarding stability of the active substance were made by the MAH. See "Overall conclusion and benefit-risk assessment".

**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, USA, or UK respectively.*

Medicinal Product

Composition
Tamsulosine HCL retard modified-release capsules 0.4 mg contain as active substance 0.4 mg of tamsulosin hydrochloride, and are light green/yellow. The capsules contain white to slightly yellowish pellets.

The capsules are packed in Al/ Starflex blister packs.

The excipients are:
Capsule core: Microcrystalline cellulose (E460), Polyacrylate, Metacrylic acid-ethyl acrylate copolymer (1:1), Polysorbate 80 (E433), Sodium laurilsulfate, Talc (E553b), and Colloidal anhydrous silica (E551).

Capsule shell: Gelatine (E441), Patent Blue V (E131), Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172), and Black iron oxide (E172).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The used excipients are well known and safe in the proposed concentrations. Their choice is justified and their functions explained. All excipients comply with the requirements in the relevant Ph.Eur. monographs. Dissolution tests have demonstrated pharmaceutical equivalence of the proposed product and the German reference product. The MAH states that no *in vivo-in vitro* correlation has been found.

Manufacturing process
The product is manufactured in four steps. The capsules are produced with sustained release matrix pellets additionally film-coated with release-controlling polymers. The product at issue is similar to the reference product in terms of chemical form, use of pellets, use of release modifying polymers and finale dosage form. Sufficient information on the process parameters has been provided. The process has been validated on three production scaled batches. The particle size of the cores is adequately controlled by the hole diameter used during the extrusion/spheronisation step. The validation results show that the process is sufficiently under control.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for colour and appearance of capsules and contents, water, identification of tamsulosin HCL, uniformity, dissolution, related substances, and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The shelf-life limits have been based on the available stability results.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 4 batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
The conditions used in the stability studies are according to the ICH stability guideline: long term, intermediate and accelerated conditions have been applied. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 24 months for the drug product is considered acceptable based on the stability data of three production scaled batches, It should be stored below 30°C as the product was shown to be unstable at accelerated conditions. Photostability studies show that the capsules should be stored in the original blister for protection against light.

Three post-approval commitments regarding stability of the medicinal product were made by the MAH. See “Overall conclusion and benefit-risk assessment.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Valid TSE certificates have been laid down for the gelatine used for the manufacturing of the capsules. No other excipient is derived from human or animal material.

II.2 Non clinical aspects

This active substance has been available on the European/Dutch market for 14 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quality of tamsulosine 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 hydrochloride is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted 3 bioequivalence studies in which the pharmacokinetic profile of the test product Tamsulosine HCl retard modified-release capsule 0.4 mg is compared with the pharmacokinetic profile of the reference product ALNA® 0.4 mg Retardkapseln. The first bioequivalence study comprises the two formulations of tamsulosin hydrochloride after single oral dose administration under fasting conditions. The second study compares the two formulations of tamsulosin hydrochloride after single oral dose administration under fed conditions. In the third study the two formulations of tamsulosin hydrochloride are compared after multiple oral dose administration (steady-state condition) under fasting conditions in healthy subjects.

In all three bioequivalence studies the same batches of test and reference product have been used. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The analytical method used in these studies, validated with respect to sensitivity, specificity, linearity, recovery, accuracy and precision (within and between days) and stability (short and long term), for determination of tamsulosin in plasma is adequate. Statistical analysis of pharmacokinetic parameters was also adequate.

It is known that food interacts with the absorption of tamsulosin hydrochloride. Therefore, a food interaction study was deemed necessary. According to the CPMP/EWP/280/96 NfG on modified-release oral and transdermal dosage forms, the effect of food should be determined after a high fat meal.

Methods

Study 1 (fasted, single dose, 0501)
A single-dose, randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 35 healthy non-smoking males (aged 18-44 years). Each subject received a single dose (0.4 mg) of one of the 2 tamsulosin hydrochloride formulations. The capsule was orally administered with 240 ml water after an overnight fast. Subjects were required to fast for 4 hours after drug administration. The washout period between treatments was 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48 and 60 hours after administration of the products. One subject withdrew for personal reasons during the 2nd period. Thirty-four subjects were eligible for pharmacokinetic analysis.

Study 2 (fed, single dose, 0428)
A single-dose, randomised, two-way crossover bioequivalence study was carried out in 40 healthy non-smoking adult male volunteers (aged 18-42 years). Thirty minutes after breakfast (1 fried egg, slice of ham (20 g), slice of cheese (20 g), slices of buttered toast (100g), glass of milk (250 ml)), each subject received a single dose (0.4 mg) of one of the 2 tamsulosin hydrochloride formulations. The breakfast can be considered as a high fat breakfast with sufficient caloric content. The capsule was orally administered with 240 ml water, after which subjects were required to fast for 4 hours. The washout period between treatments was 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 20, 24, 30, 36, 48 and 60 hours after administration of the products. One subject withdrew because of respiratory problems caused by pollen allergy. Thirty-nine subjects were eligible for pharmacokinetic analysis.

Study 3 (fasted multiple dose, 0429)
A multiple-dose, randomised, two-way crossover bioequivalence study was carried in 40 healthy non-smoking males (aged 19-44 years). After overnight (12 hours) fasting on the mornings of days 1, 2, 3, 4, 5, 6 and 7 of each period, each subject received a single dose (0.4 mg) of one of the 2 tamsulosin hydrochloride formulations. The capsule was orally administered with 240 ml water, and subjects were required to fast for 4 hours after drug administration. The washout period between treatments was 14 days.

Blood samples were collected pre-dose, before 5th, 6th and 7th drug intake, and at 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, and 24 hours after the 7th drug administration. Three subjects were withdrawn due to adverse events, and one subject withdrew for unexpected obligations. Thirty-six subjects were eligible for pharmacokinetic analysis.

Results:

Study 1: 0501
In table 1, the pharmacokinetic parameters are summarised following single dose administration under fasted conditions. AUC_{0-t} was at least 80% of $AUC_{0-\infty}$ for all subjects. The ratios of Least Square Mean (LSM) and the 90% CI for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptance range of 0.80-1.25.

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

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	168 ± 96	179 ± 105	12.5 ± 4.4	4.0 (2.0-6.0)	12.5 ± 3.8
Reference	166 ± 85	177 ± 94	13.6 ± 4.6	5.0 (1.5-6.0)	12.5 ± 4.2
***Ratio (90% CI)**	1.01 (0.93-1.08)	1.01 (0.94-1.08)	0.92 (0.84-1.00)	---	---
CV (%)	18%	17%	21%	---	---

$AUC_{0-\infty}$ 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*

Study 2: 0428

In table 2, the pharmacokinetic parameters are summarised following single dose administration under fed conditions. AUC_{0-t} was at least 80% of $AUC_{0-\infty}$ except for 2 subjects. The ratios of LSM and the 90% CI for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were within the acceptance range of 0.80-1.25.

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

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	112 ± 49	124 ± 52	7.8 ± 2.6	5.5 (4-24)	14.3 ± 6.4
Reference	117 ± 57	126 ± 60	8.3 ± 3.0	6.5 (4.5-24)	12.8 ± 3.9
***Ratio (90% CI)**	0.98 (0.92-1.03)	0.99 (0.94-1.05)	0.94 (0.87-1.01)	---	---
CV (%)	15%	15%	20%	---	---

$AUC_{0-\infty}$ 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*

Study 3: 0429

In table 3, the pharmacokinetic parameters are summarised following multiple dose administration (day 7) under fasted conditions. Predose samples taken at day 5 and day 6 indicate that steady state had been reached at day 7. The ratios of LSM and the 90% CI for $AUC_{0-\tau}$, C_{max} and C_{min} were within the acceptance range of 0.80-1.25.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of multiple-dose administration of tamsulosin hydrochloride under fasted conditions.

Treatment N=36	**$AUC_{0-\tau}$** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	173 ± 93	14.9 ± 6.0	3.4 ± 2.5	175
Reference	174 ± 103	14.9 ± 7.1	3.5 ± 2.9	171
***Ratio (90% CI)**	1.01 (0.95-1.07)	1.02 (0.93-1.12)	1.00 (0.91-1.10)	---
CV (%)	16%	25%	26%	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
$AUC_{0-\tau}$ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

Conclusion
Based on the results of the three bioequivalence studies, it can be concluded that test 0.4 mg Tamsulosin HCl Retard 0.4 mg and reference ALNA® 0.4 mg (Boehringer Ingelheim, Germany) are bioequivalent with respect to rate and extent of absorption of tamsulosin. The 90% CI for AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{0-\tau}$, C_{max}, C_{min} were all within the acceptance range of 0.80-1.25.
Tamsulosin should be taken after the same meal every day to reduce the high maximum plasma concentration (C_{max}) that would otherwise occur and which could result in an increase in adverse events. No dose-dumping was observed following single dose administration of tamsulosin under fed conditions. Therefore, it is acceptable that the multiple dose study has been performed under fasting conditions. No unexpected adverse events related to drug treatment were observed.

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).

Risk management plan
Tamsulosin hydrochloride was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of tamsulin hydrochloride 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.

Product information

SPC
The content of the SPC approved during the decentralised procedure is harmonised with the SPC of procedures FI/H/489-520. The package leaflet has been amended in response to questions of RMS and some member states.

Readability test
A readability test of a package leaflet has been sufficiently performed. The leaflet tested is a leaflet designed for a non-prescription product and the wording differs from the leaflet submitted with the initial application and also from the amended leaflet submitted with the responses. The RMS is of the opinion that the overall outcome of the test if applied to the revised leaflet would not be significantly different from the tested leaflet. In general the readability of the leaflet has not been compromised by the revisions.

The test was performed with 20 male participants aged in the range 28-79 (median 62.5 years). None had used Tamsulosin in the previous 6 months. A questionnaire of 15 questions, which addresses the most critical information for appropriate use of the product and additional important issues in each of sections 1-4 and the headline section was used. For each question it was evaluated whether participants could find the relevant information and could express it in their own words.

The user test of 20 people from the target population, in structured individual interviews, showed that the leaflet for Tamsulosin Capsules enabled 90% of participants to find, and 90% of those to express in their own words, each piece of information tested.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tamsulosine HCl retard 0.4 mg modified-release capsules have a proven chemical-pharmaceutical quality and is a generic form of ALNA® 0.4 mg Retardkapseln capsules. ALNA 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is harmonised with the SPC of FI/H/489-520. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other tamsulosin hydrochloride containing products.

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 retard 0.4 mg capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 6 June 2007. Tamsulosine HCl retard was authorised in the Netherlands on 8 May 2008.

A European harmonised birth date has been allocated, 2 July 1993 with DLP July 2008. The first PSUR will cover the period from June 2007 until July 2008. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be 6 June 2012.

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

Quality - medicinal product

- The MAH has committed to provide the results covering the whole claimed shelf-life as soon as they are available.
- The MAH has committed to perform stability testing of one European batch in bulk packaging, in order to confirm the stability in bulk and the transport conditions.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
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
LSM	Last square mean
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
Change in the name of the medicinal product in Spain.	NL/H/789/001/IB/001	IB	8-10-2007	7-11-2007	Approval	N
Change in the name of the medicinal product in Lithuania, as a result of transfer MAH.	NL/H/789/001/IB/002	IB	10-4-2008	13-5-2008	Approval	N
Change in the name of the medicinal product in Latvia, as a result of transfer MAH.	NL/H/789/001/IB/003	IB	10-4-2008	13-5-2008	Approval	N
Change in the name of the medicinal product in Estonia, as a result of transfer of MAH.	NL/H/789/001/IB/004	IB	10-4-2008	13-5-2008	Approval	N
Change address of the MAH.	NL/H/789/001/IA/005	IA	20-1-2009	3-2-2009	Approval	N