CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Flecaïnideacetaat retard 50 mg, 100 mg, 150 mg and 200 mg Teva, prolonged-release capsules Teva Nederland B.V., the Netherlands

flecainide acetate

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/2471/001-004/DC
Registration number in the Netherlands: RVG 110875-110878

14 May 2013

Pharmacotherapeutic group:	Antiarrhythmics, class IC
ATC code:	C01BC04
Route of administration:	oral
Therapeutic indication:	AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways; severe symptomatic and life-threatening paroxysmal ventricular arrhythmia; paroxysmal atrial arrhythmias (atrial fibrillation, atrial flutter and atrial tachycardia) in patients with disabling symptoms
Prescription status:	prescription only
Date of authorisation in NL:	19 November 2012
Concerned Member States:	Decentralised procedure with BE
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 Flecaïnideacetaat retard 50 mg, 100 mg, 150 mg and 200 mg Teva, prolonged-release capsules from Teva Nederland B.V. The date of authorisation was on 19 November 2012 in the Netherlands.

The product is indicated for:

- AV nodal reciprocating tachycardia; arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways, when other treatment has been ineffective.
- Severe symptomatic and life-threatening paroxysmal ventricular arrhythmia which has failed to respond to other forms of therapy. Also where other treatments have not been tolerated.
- Paroxysmal atrial arrhythmias (atrial fibrillation, atrial flutter and atrial tachycardia) in patients with disabling symptoms after conversion provided that there is definite need for treatment on the basis of severity of clinical symptoms, when other treatment has been ineffective. Structural heart disease and/or impaired left ventricular function should be excluded because of the increased risk for pro-arrhythmic effects.

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

Flecainide acetate is a Class IC antiarrhythmic agent used for the treatment of severe symptomatic life-threatening ventricular arrhythmias and supraventricular arrhythmias.
Electrophysiologically, flecainide is a local anaesthetic-type (Class IC) antiarrhythmic compound. It is an amide type of local anaesthetic, being structurally related to procainamide and encainide in so far as these agents are also benzamide derivatives.
The characterisation of flecainide as a Class IC compound is based on a triad of features: marked depression of the fast sodium channel in the heart; slow onset and offset kinetics of inhibition of the sodium channel (reflecting slow attachment to and dissociation from sodium channels); and the differential effect of the drug on the action potential duration in ventricular muscle versus Purkinje fibres, having no effect in the former and markedly shortening it in the latter. This composite of properties leads to a marked depression in conduction velocity in fibres dependant on the fast-channel fibres for depolarisation but with a modest increase in the effective refractory period when tested in isolated cardiac tissues. These electrophysiological properties of flecainide acetate may lead to prolongation of the PR-interval and QRS duration on the ECG. At very high concentrations flecainide exerts a weak depressant effect on the slow channel in the myocardium. This is accompanied by a negative inotropic effect.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Tambocor CR 50/100/150/200 mg prolonged-release capsules (NL License RVG 27131-27134) which has been registered in the Netherlands by Meda Pharma B.V. since 10 June 2002 (original product). In addition, reference is made to Tambocor authorisations in the individual member states (reference product).

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 products Flecaine 100 mg and 200 mg, prolonged release capsules, registered in France. 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 a generic application.

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 flecainide acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a very hygroscopic racemic mixture of white or almost white crystalline powder, which is soluble in water and anhydrous ethanol. No polymorphism is observed.

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

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. with additional tests for residual solvents, loss on drying and particle size.

Stability of drug substance
The retest period and packaging are included on the CEP. The retest period is 48 months with the storage condition preserved in airtight containers, protected form light, at room temperature (less than 30ºC).

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Flecaïnideacetaat retard 50 mg are gelatine opaque capsules with white body and white cap containing white or almost white round micro-tablets.
Flecaïnideacetaat retard 100 mg are gelatine opaque capsules with grey body and white cap containing white or almost white round micro-tablets.
Flecaïnideacetaat retard 150 mg are gelatine opaque capsules with grey body and grey cap containing white or almost white round micro-tablets.
Flecaïnideacetaat retard 200 mg are gelatine opaque capsules with grey body and pink cap containing white or almost white round micro-tablets.

The capsules are packed in PVC/PVDC-Aluminium blisters.

The excipients are:
All capsules: povidone, cellulose microcrystalline, crospovidone, collodial silicon dioxide, magnesium stearate, methacrylic acid-methyl methacrylate (1:2) copolymer, polyethylene glycol, talc, ethanol anhydrous;
also:
50 mg capsule: gelatin, titanium dioxide.
100 mg capsule: gelatin, titanium dioxide, black iron oxide.
150 mg capsule: gelatin, titanium dioxide, black iron oxide.
200 mg capsule: gelatin, titanium dioxide, black iron oxide and red iron oxide.

All strengths are dose proportional. The capsules contain micro-tablets which are similar for all strengths. The micro-tablets contain the active substance and the excipients

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies are: preformulation studies, formulation and process development, dissolution studies and bioequivalence studies. The discriminatory capability of the dissolution method has been demonstrated. Comparative dissolution profiles of the test and the reference product demonstrated that the dissolution profiles are comparable at pH 7.5. Dissolution profiles at pH 4.5 and 0.1N HCl were not comparable. The rationale given by the MAH is considered acceptable, as bioequivalence has been demonstrated from a clinical point of view.

Manufacturing process
The manufacturing process consists of wet granulation followed by compression of the mini-tablets followed by coating of the mini-tablets and filling the capsules with the required amount of mini-tablets, depending on the strength of the capsule. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 batches per strength.

Control of excipients
The excipients comply with the Ph.Eur. with the exception of methacrylic acid-methyl methacrylate (1:2) copolymer, for which an acceptable specification has been laid down.

Quality control of drug product
The product specification includes tests for appearance, water content, ethanol content, uniformity of dosage units, identification, assay, dissolution, degradation products and microbiological contamination.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been included for 3 full-scale batches of 50 mg and 200 mg stored at 25°C/60% RH (36 months), 30°C/65% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a transparent PVC/PVdC-Al blister pack. At all three conditions a slight increase in water content was observed. At long term conditions a very slight increase in impurities was also observed. However, all values were well within the limits. The product was demonstrated to be photostable. Based on the submitted stability data the proposed shelf life of 36 months without special storage conditions when packed in transparent PVC/PVdC-Al blisters can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only excipient of animal origin is gelatin. CEPs from the suppliers stating product compliance with TSE Guideline have been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Tambocor, which is available on the European market. 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.

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 flecainide acetate 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

Flecainide acetate 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 three bioequivalence studies in which the pharmacokinetic profile of the test product Flecaïnideacetaat retard Teva (Teva Nederland B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Flecaine L.P. prolonged-release capsules (Meda Pharma, France). The bioequivalence studies include one single-dose study with the 200 mg formulation under fasting conditions, one single-dose study under fed conditions with the 200 mg formulation and one multiple-dose study with the 100 mg formulation. According to the Note for guidance on modified release oral and transdermal dosage forms, CPMP/EWP/280/96 Corr. this approach is adequate for a modified-release multiple unit formulation with an active substance with linear pharmacokinetics.

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are 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 – 200 mg, single-dose, fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male and female subjects aged 18-47 years. Each subject received a single dose (200 mg) of one of the 2 flecainide acetate formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 4.0; 8.0; 12.0; 14.0; 16.0; 18.0; 19.0; 20.0; 21.0; 22.0; 23.0; 24.0; 25.0; 26.0; 28.0; 30.0; 36.0; 48.0; 60.0; 72.0; 96.0; 120.0 and 144.0 hours after administration of the products.

The design of the study is acceptable, the wash-out period is long enough and the sampling scheme is adequate to estimate pharmacokinetic parameters.

Results
Forty-two subjects completed the study and were analysed. Two subjects were not included in the statistic analyses; one subject due to vomiting in period II and one subject due to two consecutive missing samples during period I.
Some deviations from the study protocol were reported, five subjects took counteractive medication during the study. The MAH assessed the counteractive medication as non-clinically relevant.

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

Treatment N=42	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**T_{max}** h	**$T_{1/2}$** h	**MRT (hours)**
Test	4412 ±1727	4448 ± 1726	122 ± 47	18 (4-30)	12.3 ± 2.7	28.5 ± 4.4
Reference	4170 ± 1668	4219 ± 1670	110 ± 40	28 (8-36)	12.7 ± 2.7	33.1 ± 4.1
***Ratio (90% CI)**	1.06 (0.99-1.13)	1.06 (0.99-1.13)	1.12 (1.05-1.19)	-	-	-
CV (%)	18.0	-	17.3	-	-	-

$AUC_{0-\infty}$ 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
MRT mean residence time

**ln-transformed values*

Seven adverse events out of which one of mild intensity and six of moderate intensity occurred in seven subjects. These were no serious adverse events. The volunteers that encountered the adverse events completely recovered before the end of the study. No deaths or serious adverse events occurred in the study.

Bioequivalence study II – 200 mg, single-dose, fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 40 healthy male and female subjects aged 18-42 years. Each subject received a single dose (200 mg) of one of the 2 flecainide acetate formulations with 200 ml of water, under fed conditions. A standardized 800 kilocalories continental breakfast was served 30 minutes before dosing. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 4.0; 8.0; 12.0; 14.0; 16.0; 18.0; 19.0; 20.0; 21.0; 22.0; 23.0; 24.0; 25.0; 26.0; 28.0; 30.0; 36.0; 48.0; 60.0; 72.0; 96.0; 120.0 and 144.0 hours after administration of the products.

The design of the study is acceptable, the wash-out period is long enough and the sampling scheme is adequate to estimate pharmacokinetic parameters. The composition of the meals is according to the guideline.

Results
All subjects completed the study and were included in the analysis.

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

Treatment N=40	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	T_{max} h	$T_{1/2}$ h	MRT (hours)
Test	4595 ± 2065	4633 ± 2072	116 ± 42	16 (4-36)	14.1 ± 3.5	30.1 ± 4.8
Reference	4715 ± 2010	4758 ± 2021	124 ± 48	18 (12-30)	14.1 ± 3.8	31.4 ± 5.2
***Ratio (90% CI)**	0.97 (0.92-1.01)	0.97 (0.92- 1.01)	0.94 (0.89- 0.99)	-	-	-
CV (%)	12.1		13.5	-	-	-

$AUC_{0-\infty}$ 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
MRT mean residence time

**ln-transformed values*

Nine adverse events out of which eight of mild and one of moderate intensity occurred in five subjects. These were not serious adverse events. The volunteers that encountered the adverse events completely recovered before the end of the study. No difference between the treatments was observed.

Conclusion on study I and II
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 flecainide acetate under fasted conditions, it can be concluded that Flecaïnideacetaat retard 200 mg Teva and Flecaine L.P. 200 mg prolonged-release capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study III – 100 mg, multiple-dose, fasted conditions
Design
A two period, cross-over, block randomized, multiple dose bioequivalence study (at steady state) was carried out under fasted conditions in 36 healthy male and female subjects aged 19-44 years. The test product and reference product were administered with 200 ml water, in the morning under fasting conditions, during five days. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were taken before dosing in Days 1 to 5 and, only in Day 5 at 1.0; 2.0; 4.0; 6.0; 8.0; 10.0; 12.0; 14.0; 15.0; 16.0; 17.0; 18.0; 19.0; 20.0; 21.0; 22.0; 23.0 and 24.0 hours post dose after each administration.

The design of the study is acceptable, the wash-out period is long enough and the sampling scheme is adequate to estimate pharmacokinetic parameters.

Results
Two subjects were excluded from pharmacokinetic and statistic evaluation due to vomiting occurring before twice the median T_{max}. Thirty-four subjects completed the study and were included in the analysis.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=34	C_{minss} (ng/ml)	C_{maxss} (ng/ml)	AUC_{ss} (ng/ml*h)	%ptf	T_{maxss} (hours)	%Swing	Caverage (ng/ml)
Test	67 ± 27	99 ± 31	2024 ± 661	40 ± 16	10 ± 4	56 ± 32	84 ± 27

Reference	70 ± 25	105 ± 38	2134 ± 732	39 ± 15	10 ± 4	52 ± 27	89 ± 31
***Ratio (90% CI)**	0.93 (0. 88- 0.99)	0.95 (0.89- 1.02)	0.95 (0.90- 1.01)	1.02 (0. 88- 1.18)	-	-	-
CV (%)	14.4	16.0	14.2	36.0	-	-	-

**In-transformed values*

Seven adverse events out of which four of mild and three of moderate intensity occurred in six subjects. These were no serious adverse events. The volunteers that encountered the adverse events completely recovered before the end of the study.

Conclusion on study III

The 90% confidence intervals calculated for AUC_{0minss}, $AUC_{maxss,}$ AUCss and &ptf 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 flecainide acetate at steady state, it can be concluded that Flecaïnideacetaat retard 100 mg Teva and Flecaine L.P. 100 mg prolonged-release capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Biowaiver

Waiving of the results of the bioequivalence studies to the other strengths is considered justified since the formulation is a multiple unit formulation with an active substance with linear pharmacokinetics. All strengths are qualitatively and quantitatively proportional and show similar dissolution characteristics.

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

Flecainide acetate was first approved in 1982, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of flecainide acetate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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 MAH has adapted the SPC to the SPC of another flecainide acetate generic. Additionally the agreed wording from the established CSP was included (NO/H/PSUR/0005/001).

Readability test

The package leaflet 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, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There were sufficient questions about the critical sections. Overall, each and every question meets the criterion of 81% correct answers The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Flecaïnideacetaat retard 50 mg, 100 mg, 150 mg and 200 mg Teva, prolonged-release capsules have a proven chemical-pharmaceutical quality and are generic forms of Tambocor CR 50/100/150/200 mg prolonged-release capsules. Tambocor 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, package leaflet and labelling are in the agreed templates and are in agreement with other flecainide acetate 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 Flecaïnideacetaat retard 50 mg, 100 mg, 150 mg and 200 mg Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 5 June 2012. Flecaïnideacetaat retard 50 mg, 100 mg, 150 mg and 200 mg Teva, prolonged-release capsules were authorised in the Netherlands on 19 November 2012.

The date for the first renewal will be: 5 June 2017.

The following post-approval commitment has been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to perform the validation of the stability studies and manufacturing process for the first three industrial batches per strength. This commitment is noted.

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
CSP	Core Safety Profile
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
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
PTF	Peak-trough Fluctuation
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
Name change of the product in Belgium.	NL/H/2471/ 001-004/IB/ 001	IB	10-12-2012	9-1-2013	Approval	N