CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Repaglinide STADA 0,5 mg, 1 mg, 2 mg, and 4 mg tablets Stada Arzneimittel AG, Germany

repaglinide

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/1455/001- 004/DC
Registration number in the Netherlands: RVG 103352,103355,103356,103357

19 March 2010

Pharmacotherapeutic group:	other blood glucose lowering drugs, excl. insulins
ATC code:	A10BX02
Route of administration:	oral
Therapeutic indication:	type 2 diabetes, when hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise; in combination with metformin: type 2 diabetes in patients who are not satisfactorily controlled on metformin alone.
Prescription status:	prescription only
Date of authorisation in NL:	2 December 2009
Concerned Member States:	Decentralised procedure with AT, BE, BG, DE, ES, FI, FR, LU, RO, SE, SI, and IT (only 0.5 mg, 1 mg, and 2 mg)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) and 10(3) (only 4 mg)

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 Repaglinide STADA 0,5 mg, 1 mg, 2 mg, and 4 mg tablets, from Stada Arzneimittel AG. The date of authorisation was on 2 December 2009 in the Netherlands. Repaglinide is indicated in patients with type 2 diabetes (Non Insulin-Dependent Diabetes Mellitus (NIDDM)) whose hyperglycaemia can no longer be controlled satisfactorily by diet, weight reduction and exercise. Repaglinide is also indicated in combination with metformin in type 2 diabetes patients who are not satisfactorily controlled on metformin alone.
Treatment should be initiated as an adjunct to diet and exercise to lower the blood glucose in relation to meals.

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

Repaglinide is a novel short-acting oral secretagogue. Repaglinide lowers the blood glucose levels by stimulating the release of insulin from the pancreas, an effect dependent upon functioning β-cells in the pancreatic islets. Repaglinide closes ATP-dependent potassium channels in the β-cell membrane via a target protein different from other secretagogues. This depolarises the β-cell and leads to an opening of the calcium channels. The resulting increased calcium influx induces insulin secretion from the β-cell.
In type 2 diabetic patients, the insulinotropic response to a meal occurred within 30 minutes after an oral dose of repaglinide. This resulted in a blood glucose-lowering effect throughout the meal period. The elevated insulin levels did not persist beyond the time of the meal challenge. Plasma repaglinide levels decreased rapidly, and low drug concentrations were seen in the plasma of type 2 diabetic patients 4 hours post-administration. A dose-dependent decrease in blood glucose was demonstrated in type 2 diabetic patients when administered in doses from 0.5 to 4 mg repaglinide. Clinical study results have shown that repaglinide is optimally dosed in relation to main meals (preprandial dosing). Doses are usually taken within 15 minutes of the meal, but the time may vary from immediately preceding the meal to as long as 30 minutes before the meal.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product NovoNorm 0,5 mg, 1 mg, and 2 mg tablets (EU Licences EU/1/98/076/004-7, EU/1/98/076/011-4, and EU/1/98/076/018-22, respectively) which have been registered through a centralised procedure by Novo Nordisk since 1998.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC for the 0,5 mg, 1 mg and 2 mg tablets. The marketing authorisation for 4 mg tablets is granted based on article 10 (3) of Directive 2001/83/EC, as this stength is not registered by the originator.

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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product NovoNorm 2 mg tablets, registered in Denmark. 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 repaglinide, an established active substance described in the European Pharmacopoeia (Ph. Eur.*). The active substance is a white to almost white powder and is practically insoluble in water but is freely soluble in methanol and in methylene chloride. Repaglinide shows polymorphism and is a single enantiomer, the other enantiomer is limited in the drug substance. The drug substance manufacturers manufacture polymorphic form I and the S-isomer.

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 repaglinide differs for all manufacturers, in general the manufacturing process has been adequately described. No class 1 solvents or heavy metal catalysts are used by any of the DMF-holders. The active substance has been adequately characterised and in general acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
All drug substance manufacturers and the MAH have adopted the Ph.Eur. specifications, with additional requirements for polymorphic form and residual solvents. The absence of any other polymorphic forms has been confirmed by X-Ray powder diffraction. The active substance repaglinide conforms to that of Form I. The MAH also has an additional requirement for particle size. In general the specifications are acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for all manufacturers.

Stability of drug substance
Sufficient stability data on the active substance have been provided for all drug substance manufacturers, and the applicant has adopted their respective re-test periods.

** 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
The drug product is an uncoated immediate release tablet, available in four different strengths. The 4 mg strength contains a breaking notch on both sides, so it can be divided into equal halves. The appearance of the 0.5 mg, 1 mg, and 2 mg strength tablets are almost identical, i.e. white, round and biconvex with the same thickness for the 0.5 mg and 1.0 mg and a slightly thicker 2 mg, the 1.0 mg tablet is imprinted with "1" and the 2.0 mg tablet is imprinted with "2", so the tablets can be distinguished.

The tablets are packaged in an OPA-Al-PVC/Al blister enclosed in an outer carton..

The excipients are: microcrystalline cellulose, poloxamer 188, croscarmellose sodium, and magnesium stearate.
The excipients and packaging are usual for this type of dosage form.

The content of excipients of the 0.5 mg and 1.0 mg tablets are the same as are the contents of the 2.0 and 4.0 tablet formulations. The only difference is the amount of active substance. The 1.0 mg and 2,0 mg formulation are completely dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients has been justified and their functions explained. The main development studies performed were in respect to the manufacturing process development and comparison of dissolution profiles with the originator product. The choices of the packaging and manufacturing process are justified. In general the pharmaceutical development of the product has been adequately performed.

Comparative dissolution was performed for both Repaglinide 2 mg tablets and the reference product NovoNorm 2 mg tablets, for the batches used in the bioequivalence studies, in 0.1N HCl, Acetate buffer pH 4.5 and Phosphate buffer pH 6.8 with a paddle apparatus at 75 rpm. In the 0.1 N HCl both the test and reference product dissolve very rapidly, i.e. more than 85% in less than 15 minutes. In the buffers pH 4.5 and 6.8, the dissolution profiles are considered similar.

Excipients
The excipients comply with the Ph.Eur. All specifications are acceptable.

Breakability:
Breakability testing has been performed for the 4mg strength in accordance with the Ph.Eur monograph test for subdivision of a tablet and all test results were within the specified limits.

Manufacturing process
The manufacturing process consists mainly of blending and tablet compressing. The manufacturing process is considered a non-standard process given the low amount of drug per tablet. Process validation data on the product has been presented for two pilot scale batches and one production scale batch of the 0.5, 1 and 2 mg strengths and three pilot scale batches of the 4 mg strength.

Quality control of drug product
The product specification includes tests for appearance, identity, diameter, average tablet mass, assay, uniformity of dosage units, related substances, disintegration, dissolution and microbial limits. The release and shelf-life requirements are identical. The specifications are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on pilot scale batches of all strengths, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 5 pilot scale batches of the 0.5 mg, 1 mg, and 2 mg strengths and for 3 batches of the 4 mg strength. All batches were stored at 25°C/60%RH (18 months),

30°C/65% RH (12 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 OPA-Al-PVC/Al blisters. A method for the control of the enantiomer, has been included. No changes are seen under all conditions. The proposed shelf life of 30 months in the proposed packaging is justified.
The MAH has committed to perform a post-approval stability study on two batches of the 0.5 mg and 2 mg strengths and respectively on one production batch for the 1 mg strength. In addition, the MAH has committed to perform a post-approval stability study on two batches of the 4 mg strength, only if production batches will be produced. Due to planned 60 months stability study the available stability results will be reported at the time of renewal of marketing authorisation.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A declaration has been provided for the the excipient magnesium stearate to confirm the vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of NovoNorm, 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 repaglinide 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

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

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Repaglinide STADA 2 mg tablets (STADA Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product NovoNorm 2 mg tablets (Novo Nordisk, Denmark).

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 (if applicable) in different member states.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
A monocentre, open, randomised, single dose, two period, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male volunteers, aged 18-54 years of normal weight. Each subject received a single dose (2 mg) of one of the 2 repaglinide formulations. The tablet was orally administered with 240 ml water after a 10 hour overnight fasting period. A standard meal (composition provided) was given 4 hours upon dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.1, 0.2, 0.3, 0.4, 0.5,1, 1.15, 1.3, 2, 2.3, 3, 4, 5, 6, 7 and 9 hours after administration of the products. The analytical method is adequate 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
Twenty-two non-serious adverse events were reported after administration of the test product. Fourteen non-serious adverse events were reported after administration of the reference product. All subjects completed both periods of the study and the pharmacokinetic variables were calculated of all 60 subjects. One subject was excluded from statistical analysis for being an outlier. The plasma concentrations of this subject were about 10% after administration of the reference product compared with the mean value of all subjects. This resulted in a ratio of the AUC of 18.6 and for C_{max} 12.5. No protocol violation could justify these low concentrations. According to the Q and A document on the guideline on Investigations of Bioavailability and Bioequivalence, statistical drop out is not allowed in bioequivalence studies. However, from the submitted results it is clear that the problem with this subject is with the reference product and not with the test product. Therefore, 59 subjects were statistically evaluated for the bioequivalence study.

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

Treatment N=59	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	57.8 ± 27.3	59.5 ± 27.9	43.6 ± 13.8	0.67 (0.33-1.00)	2.9 ± 1.5
Reference	59.5 ± 30.2	60.9 ± 30.8	38.3 ± 14.3	0.83 (0.33-3.00)	2.5 ± 0.8
***Ratio (90% CI)**	0.98 (0.89 - 1.08)	0.98 (0.89 - 1.08)	1.16 (1.06 - 1.26)	---	---
CV (%)	32.1	Not reported	28.8	---	---

$AUC_{0-\infty}$ 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 submitted bioequivalence study shows that the product to be registered is not bioequivalent with NovoNorm 2 mg tablets as the 90% confidence interval of C_{max} was outside the acceptance range of 0.80 – 1.25. The MAH did consider Replaginide as a highly variable drug for which the acceptance criteria could be widened post-hoc. However, this was not endorsed by the RMS and the Member states. The CV for C_{max} is less than 30%, indicating that repaglinide can not be classified as a highly variable drug.

Therefore, the MAH submitted a second bioequivalence study This second study was of identical design as the first, performed with the same batch of the test product, but with a different batch of NovoNorm 2 mg.

Bioequivalence study with other reference batch
A monocentre, open, randomised, single dose, two period, crossover bioequivalence study was carried out under fasted conditions in 72 healthy male volunteers, aged 18-55 years of normal weight. Each subject received a single dose (2 mg) of one of the 2 repaglinide formulations. The tablet was orally administered with 240 ml water after a 10 hour overnight fasting period. Water was allowed till 1 hour before drug administration. A standard meal (composition provided) was given 4 hours upon dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.1, 0.2, 0.3, 0.4, 0.5,1, 1.15, 1.3, 2, 2.3, 3, 4, 5, 6, 7 and 9 hours after administration of the products. The analytical method is adequate 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

A total number of 44 non-serious adverse events (AE) were registered in 29 volunteers: 1 AE before dosing, 23 AEs after administration of the test product and 20 AEs after administration of the reference product. All adverse events were regarded as not serious, all AEs resolved completely within short time frame. The results of laboratory screening gave no indications for adverse events or adverse drug reactions. All subjects completed both periods of the study and the pharmacokinetic variables were calculated of all 72 subjects.

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

Treatment N=72	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	62.9 ± 31.6	64.2 ± 32.3	43.7 ± 16.9	0.73 (0.33 – 3.00)	1.8 ± 0.9
Reference	63.8 ± 25.8	65.1 ± 26.4	43.0 ± 15.7	0.78 (0.33 – 2.00)	1.9 ± 1.5
***Ratio (90% CI)**	0.91 (0.81 – 1.04)	---	0.98 (0.87 – 1.09)	---	---
CV (%)	47.9	---	42.2	---	---

$AUC_{0-\infty}$ 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}, 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 repaglinide under fasted conditions, it can be concluded that Repaglinide STADA 2 mg tablets and the NovoNorm 2 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
Repaglinide is to be taken before meals and it is stated in the SPC that food has no influence on the pharmacokinetics. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation of results

The waiving of bioequivalence studies for the 0.5 mg, 1 mg, and 4 mg strengths have been adequately justified. Therefore the results of the bioequivalence study performed with the 2 mg tablets also apply to the other strengths. The 1 mg formulation is dose proportional.
The results of the bioequivalence study with the 2 mg strength also apply to the 0,5 and 4 mg tablets. A biowaiver could be granted, as the following requirements were met:

- the pharmaceutical products are manufactured by the same manufacturer and process.
- the pharmacokinetics of repaglinide has been shown to be linear over the therapeutic range.
- the quantitative composition of the different strengths is the same and the tablets are containing a low concentration of the active substance (less than 5%).
- the dissolution profile should be similar under identical conditions for the additional strengths and the strength of the biobatch.

The MEB has been assured that the bioequivalence study 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).

Risk management plan

Repaglinide was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of repaglinide 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 SPC is in accordance with the most recent SPC of NovoNorm tablets. The only difference in the SPC for NL/H/1455/01-04/DC are the different pack sizes in section 6.5 of the SPC.

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 round with 3 subjects and a testing round with 20 subjects. The test included 15 questions on the text of the leaflet and 4 questions on general impressions, layout and improvements. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There were sufficient questions about the critical sections. The test results were satisfactory; all questions were located and answered correctly by at least 90% of the subjects. Therefore, no changes were made to the leaflet as a result of the user test. The readability test itself and the evaluation report are of an acceptable quality. The conclusions are clear and concise.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Repaglinide STADA 0,5 mg, 1 mg, 2 mg, and 4 mg tablets a proven chemical-pharmaceutical quality and are a generic form of NovoNorm 0.5 mg, 1 mg, and 2 mg tablets. Novonorm 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 consistent with that of the reference product. 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Repaglinide STADA tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 September 2009. Repaglinide STADA was authorised in the Netherlands on 2 December 2009.

A European harmonised birth date has been allocated (31 December 1997) and subsequently the first data lock point for repaglinide is 31 December 2010. Therefore, the first PSUR of repaglinide will cover the period from approval until 31 December 2010. Thereafter, a 3-yearly PSUR cycle will apply.

The date for the first renewal will be: 1 September 2014.

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

Medicinal product

- The has committed to submit a type IB variation after finalisation of the procedure for change in product name in the Member states. This commitment has been fulfilled by submission of variation NL/H/1455/001-004/IB/001. See '*Steps taken after the finalisation of the initial procedure'* table on page 11.

Quality - medicinal product

- The MAH has committed to perform a post-approval stability study on two batches of the 0.5 mg and 2 mg strengths and respectively on one production batch for the 1 mg strength. In addition, the MAH has committed to perform a post-approval stability study on two batches of the 4 mg strength, only if production batches will be produced. Due to planned 60 months stability study the available stability results will be reported at the time of renewal of marketing authorisation.

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
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NIDDM	Non Insulin-Dependent Diabetes Mellitus
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.	NL/H/1455/ 001-004/IB/ 001	IB	29-12-2009	28-1-2010	Approval	N
Change in the name and/or address of a manufacturer of the active substance where no Ph. Eur. Certificate for Suitability is available. New manufacturer (replacement or addition).	NL/H/1455/ 001-004/IB/ 002	IB	29-12-2009	28-1-2010	Approval	N