CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Gliclazide Sandoz retard 30 mg, modified-release tablets
Sandoz B.V., the Netherlands

gliclazide

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/1700/001/DC
Registration number in the Netherlands: RVG 105042

14 September 2010

Pharmacotherapeutic group:	Sulfonamides, urea derivatives
ATC code:	A10BB09
Route of administration:	oral
Therapeutic indication:	Non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.
Prescription status:	prescription only
Date of authorisation in NL:	2 August 2010
Concerned Member States:	Decentralised procedure with AT, BE, BG, EE, ES, FR, HU, PL, PT, 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 Gliclazide Sandoz retard 30 mg, modified-release tablets, from Sandoz B.V. The date of authorisation was on 2 August 2010 in the Netherlands. The product is indicated for treatment of Non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

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

Gliclazide is a hypoglycaemic sulphonylurea oral antidiabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.
Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β-cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment. In addition to these metabolic properties, gliclazide has haemovascular properties.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Diamicron 30 mg tablets which has been registered in the UK by Servier Laboratories Limited since 7 December 2001. In the Netherlands, The reference medicinal product authorised for not less than 10 years is Diamicron 80 mg tablets (NL License RVG 06702), which has been registered since 25 September 1974. Diamicron 30 mg modified-release tablets (NL License RVG 25617) has been registered since 13 April 2001 by procedure FR/H/0171/001/MR. In addition, reference is made to Diamicron authorisations in the individual member states.

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 Diamicron 30 mg modified-release tablets, registered in the UK. 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 gliclazide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Gliclazide is a white to almost white powder, which is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and slightly soluble in ethanol. The drug substance is not hygroscopic, there are no known polymorphs and it has no chiral centres.

The CEP procedure is used for both suppliers of 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 new 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 CEP, with additional requirements for particle size. The specification is 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 2 full-scale batches from both manufacturers

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH and 40°C/75% RH. At both conditions no changes or trends are observed in the tested parameters. The proposed retest period of 1 year for both suppliers without any special storage requirement is justified.

** 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
Gliclazide Sandoz retard 30 mg is a white, oval, biconvex tablet, imprinted with “GLI 30” on one side.

The modified-release tablets are packed in Alu/PVC blister packs or HDPE bottles with screw cap with a tamper evident ring and mounted desiccant capsule.

The excipients are: hypromellose, calcium hydrogen phosphate dihydrate, lactose monohydrate, colloidal anhydrous silica, sodium stearyl fumarate.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Pharmaceutical development studies were performed in order to optimize the matrix

system for controlling the release rate, filler-binder ratio and lubricant type. The choices of the packaging materials and manufacturing process are justified. Furthermore, comparative dissolution studies were performed. The MAH demonstrated comparable results for assay and impurity profiles for Diamicron MR 30 mg tablets from eight different EU countries and four batches of the generic drug product. The dissolution profiles of the biobatch were shown to be similar to the originator at pH values.
Bioequivalence studies were performed by comparing the test batch with the originator Diamicron product. The test batch was manufactured according to the finalized batch formula. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of sieving, blending, slugging (compressing), milling, blending and compression into tablets. The manufacturing process has been adequately validated according to relevant European guidelines. The process is considered non-standard. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with the requirements of the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, loss on drying, identification, assay, uniformity of dosage units, dissolution, related substances and microbial quality. Except for loss on drying, assay and related substances, the release and shelf-life requirements are identical. The proposed specifications for the drug product are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on four full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on four full-scale batches stored at 25°C/60% RH (18 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 Al/Al-blisters and HDPE bottles. Except for an increase in impurities, no changes or trends were observed at both storage conditions.
A sun test was performed in accordance with ICH recommendations on two batches of unpacked tablets showing only a slight increase of total impurities. As no significant changes in the stability parameters were detected, the product is considered to be photostable.
The granted shelf life, packaging material and storage conditions are: 24 months in Al-Al blisters or HDPE bottles; ‘This medicinal product does not require any special storage conditions’.
The MAH committed to continue the ongoing stability studies up to the proposed shelf-life (24 months) in accordance with the stability protocol.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only material of animal origin used in the manufacture of the drug product. The manufacturer of lactose certifies that the milk is sourced from healthy animals under the same conditions as milk collected for human consumption.

II.2 Non clinical aspects

This product is a generic formulation of Diamicron, 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 gliclazide 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

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

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the test product Gliclazide Sandoz retard 30 mg, modified-release tablets (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Diamicron 30 mg modified-release tablets (Servier Laboratoires Limited, UK). One single dose study under fed conditions, one single dose study under fasted conditions and one multiple dose study under fed conditions were conducted.

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 I – single-dose, fed
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 26 healthy non-smoking male subjects, aged 20-53 years. Each subject received a single dose (30 mg) of one of the 2 gliclazide formulations.
The high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) breakfast was derived approximately of 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The high-calorie, high-fat breakfast consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, approximately four ounces of hash brown potatoes and approximately eight ounces of whole milk. Standardized caffeine-free/xanthine-free meals were provided to subjects at least 4 hours after drug administration in each period. Further standardized meals were served at scheduled times throughout the remainder of each study confinement period. Other than the optional pre-study snack and the protocol specified meals, subjects were not allowed any other food or beverage (except for water) while confined in the clinic. With the exception of the water ingested during drug administration and the fluids with breakfast, water was not permitted from 1 hour prior to drug administration until 1 hour post-dose, after which water was permitted *ad libitum*. Glucose administration (in the form of 60 mL of grape juice) was administered to subjects 1 hour after the high-fat, high-calorie breakfast and repeated every 30 minutes (t5 minutes) until 10 hours after dosing to prevent hypoglycemia. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5 , 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, 24, 36, 48, 60 and 72 hours after administration of the products.

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

Results
One subject withdrew prior to period two for personal reasons and one subject due to an adverse event prior to period two (feeling hot). The samples of all 24 volunteers who completed the study were included in the analysis.

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

Treatment	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	t_{max}	$t_{1/2}$

N=24	ng.h/ml	ng.h/ml	ng/ml	h	h
Test	16373 ± 6669	17824 ± 7921	1028 ± 273	5.5 (3-11)	14.6 ± 5.6
Reference	16771± 6704	17878 ± 7276	1013 ± 337	6 (4.5-10)	14.0 ± 4.1
***Ratio (90% CI)**	0.97 (0.93-1.02)	0.99 (0.94-1.03)	1.03 (0.96-1.11)	-	-
CV (%)	8.7	9.0	15	-	-

$AUC_{0-\infty}$ 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*

Bioequivalence study II – multiple-dose, fed

Design

A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 26 healthy non-smoking male subjects, aged 21-54 years. Each subject received a single dose (30 mg) per day of one of the 2 gliclazide formulations from day 1 until day 6.

Subjects were confined to clinical facility from at least 14 hours prior to the first dosing on Day 1 until at least 24 hours after the last dose on Day 7, for a total of at least 158 hours for each study period. In each period, an optional pre-study snack was provided to each subject after check-in and prior to fasting. Subjects fasted for at least 10 hours prior to the start of the high-fat, high-calorie breakfast and for at least 4 hours following drug administration. Subjects were Sewed a high-fat, high calorie breakfast 30 minutes prior to drug administration. Subjects were required to finish the meal in 30 minutes or less.

The high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) breakfast was derived approximately of 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. The high-calorie, high-fat breakfast consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, approximately four ounces of hash brown potatoes and approximately eight ounces of whole milk.

Standardized caffeine-free/xanthine-free meals were provided to subjects at least 4 hours after each drug administration in each period. Further standardized meals were served throughout the remainder of the confinement period. Other than the optional pre-study snack and the protocol specified meals subjects were not allowed any food or beverage (except for water) while confined in the clinic. With the exception of the water ingested during drug administration, the fluids with breakfast and glucose solution, water was not permitted from 1 hour prior to drug administration until 1 hour post dose, after which water was permitted *ad libitum.*

Glucose administration (in the form of 60 mL of grape juice) was administered to subjects 1 hour after the high-fat, high-calorie breakfast and repeated every 30 minutes (+5 minutes) until 10 hours afler dosing to prevent hypoglycemia.

There were 2 dosing periods, separated by a washout period of 7 days.

In each period, a total of 24 blood samples were collected, Pre-dose samples on day 1, 4, and 5. At day 6, blood samples were collected pre-dose and at 0.5 and 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16 and 24 hours after drug administration.

Analytical/statistical methods

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

Results
Two subjects dropped out both for personal reasons (one in period 2 on day 4 and one in period 1 on day 3). The samples of all 24 volunteers who completed the study were included in the analysis.

Table 2. Pharmacokinetic parameters in steady state (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of gliclazide after multiple doses under fed conditions.

Treatment N=24	**$AUC_{0-\tau,ss}$** ng/ml/h	**$C_{max,ss}$** ng/ml	**$C_{min,ss}$** ng/ml	**PTF** %
Test	19752 ± 6743	1562± 437	454 ± 202	143
Reference	19771 ± 6424	1384 ± 407	479 ± 199	116
***Ratio (90% CI)**	0.99 (0.97-1.01)	1.12 (1.07-1.18)	0.93 (0.90-0.96)	-
CV (%)	4.6	9.3	6.9	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence studies I and II
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} after single dosing, and for $AUC_{0-\tau,ss}$ $C_{max,s}$ and $C_{min,ss}$ after multiple dosing 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 gliclazide under fed conditions, it can be concluded that Gliclazide Sandoz retard 30 mg and Diamicron 30 mg, modified-release tablets are bioequivalent with respect to rate and extent of absorption.

However, both studies were performed under fed conditions. This is not considered acceptable as the effect of food on the pharmacokinetics of the test tablets has to be shown as well, according to the note for guidance on modified release oral and transdermal dosage forms section II (Pharmacokinetic and Clinical evaluation (CPMP/EWP280/96)). Therefore the MAH was required to perform a single-dose fasted study to provide the required information of food on the pharmacokinetics of gliclazide.

<u>Bioequivalence study III – single-dose, fasted</u>
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 19-55 years. Each subject received a single dose (30 mg) of one of the 2 gliclazide formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Study subjects fasted at least four hours after drug administration. Glucose administration in the form of 20 % glucose solution (60 mL) was administered to subjects at 1, 2 and 3 hours after dosing (± 10 minutes) to prevent hypoglycaemia under fasting conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 24, 36, 48, 60, 72 and 96 hours after administration of the products.

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

Results
One subject withdrew for personal reasons and one subject due to an adverse event (high temperature, loose stool and nausea). The samples of all 28 volunteers who completed the study were included in the analysis.

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

Treatment N=28	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	21986 ± 7140	23355 ± 8101	876 ± 221	10 (5-16)	18 ± 7
Reference	22726 ± 8001	24011 ± 8591	903 ± 209	9 (5-12)	17 ± 5
***Ratio (90% CI)**	0.98 (0.94-1.02)	0.98 (0.94-1.02)	0.97 (0.91-1.03)	-	-
CV (%)	9.1	8.6	13.7	-	-

$AUC_{0-\infty}$ 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 gliclazide under fasted conditions, it can be concluded that Gliclazide Sandoz retard 30 mg and Diamicron 30 mg, modified-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.

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
Gliclazide was first approved in 1972, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of gliclazide 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Diamicron. As for the reference product, a warning was included about the conversion from the conventional 80 mg formulation to the presented 30 mg XR formulation.

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 two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Gliclazide Sandoz retard 30 mg, modified-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Diamicron 30 mg modified-release tablets. Diamicron 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 gliclazide 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 Gliclazide Sandoz retard 30 mg, modified-release tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 June 2010. Gliclazide Sandoz retard 30 mg, modified-release tablets was authorised in the Netherlands on 2 August 2010.

A European harmonised birth date has been allocated (1 January 1972) and subsequently the first data lock point for gliclazide is February 2011. The first PSUR will cover the period from June 2010 to February 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 22 November 2014.

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

Quality - medicinal product

- The MAH committed to continue the ongoing stability studies up to the proposed shelf-life (24 months) in accordance with the stability protocol.

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
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