CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ristidic 1.5 mg, 3.0 mg, 4.5 and 6.5 mg capsules, hard
ICN Polfa Rzeszow S.A., Poland

rivastigmine hydrogen tartrate

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/1542/001-004/DC
Registration number in the Netherlands: RVG 103326-103329

11 May 2010

Pharmacotherapeutic group:	anti-dementia drugs, anticholinesterases
ATC code:	N06DA03
Route of administration:	oral
Therapeutic indication:	symptomatic treatment of mild to moderately severe Alzheimer's dementia; symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.
Prescription status:	prescription only
Date of authorisation in NL:	4 November 2009
Concerned Member States:	Decentralised procedure with BG, CZ, HU, PL, RO, 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 Ristidic 1.5 mg, 3.0 mg, 4.5 and 6.5 mg capsules, hard, from ICN Polfa Rzeszow S.A. The date of authorisation was on 4 November 2009 in the Netherlands.

The product is indicated for:

- symptomatic treatment of mild to moderately severe Alzheimer's dementia.
- symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

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

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Exelon 1.5, 3, 4.5 and 6 mg capsules, hard which has been registered in the European Union through procedure EU/1/98/066 by Novartis Europharm Ltd. since 12 May 1998.

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

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the 1.5 and 6 mg products is compared with the pharmacokinetic profile of the reference product Exelon 1.5 mg and 6 mg hard capsules, registered in the European Union. 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. These generic products can be used instead of their reference products.

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 these product types 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 rivastigmine hydrogen tartrate, an established active substance not described in the European, Britisch or US Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white powder, very hygroscopic and is very soluble in water and soluble in methanol. Rivastigmine hydrogentartrate is manufactured as the S-enantiomer.

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.

Manufacturing process
The manufacturing process consists of four steps. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification is has been established in-house by the MAH. The specification is considered 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 3 full-scale batches. Chiral purity is confirmed by HPLC. The method was sufficiently validated.

Stability of drug substance
Stability data on the active substance have been provided for 6 production-scale batches stored at 25°C/60% RH (up to 60 months) and for 3 production scale batches at 40°C/75% RH (6 months). The batches were adequately stored. No changes are seen during the tested period for both storage conditions. The proposed re-test period of 24 months with no additional storage requirements could be granted.

* *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
Ristidic 1.5 mg contains as active substance rivastigmine hydrogen tartrate corresponding to rivastigmine 1.5 mg and is a yellow/yellow hard gelatine capsule imprinted with "RIVA 1.5mg" on body with black ink containing white to off-white granular powder.

Ristidic 3.0 mg contains as active substance rivastigmine hydrogen tartrate corresponding to rivastigmine 3 mg and is a light orange/light orange hard gelatine capsule imprinted with "RIVA 3mg" on body with black ink containing white to off-white granular powder.

Ristidic 4.5 mg contains as active substance rivastigmine hydrogen tartrate corresponding to rivastigmine 4.5 mg and is a caramel/caramel hard gelatine capsule imprinted with “RIVA 4.5mg” on body with black ink containing white to off-white granular powder.

Ristidic 6.0 mg contains as active substance rivastigmine hydrogen tartrate corresponding to rivastigmine 6 mg and is a light orange/caramel hard gelatine capsule imprinted with “RIVA 6mg” on body with black ink containing white to off-white granular powder.

The hard capsules are packed in transparent PVC/Aluminium blisters.

The excipients are:

Capsule content -	microcrystalline cellulose E460, hypromellose E464, colloidal anhydrous silica E551, magnesium stearate E572.
Capsule shell -	yellow iron oxide E172, titanium dioxide E171, gelatin E441, iron oxide red E172 (only for the 3.0, 4.5 & 6.0 mg capsule shells)
Printing ink -	shellac, propylene glycol concentrated ammonia solution, iron oxide black, potassium hydroxide.

The quantitative composition of the capsules is not dose proportional, but the ratio between the amounts of excipients is similar with a small difference in microcrystalline cellulose to compensate the difference of active substance. This is in line with the NfG on the Investigation of Bioavailability and Bioequivalence for preparations containing a low concentration of the active substance (less than 5 %).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were the investigation of the originator product Exelon for composition and dissolution profiles. The choices of the packaging and manufacturing process were properly justified. The different strengths of the drug product show a similar dissolution profile in media of pH 1.2, 6.8 and in water. A fast dissolution of more than 85 % in 15 minutes is shown for all capsule strengths. For the bioequivalence studies, the 1.5 and 6.0 mg capsules were compared with the originator Exelon 1.5 mg and 6.0 mg capsules. The composition of the biobatch is similar to the final product. The pharmaceutical development of the product has been adequately performed. Pharmaceutical equivalence was sufficiently shown.

Manufacturing process

The manufacturing process consists of pre-mixing, wet granulation, drying, sizing, final mixing and capsule filling. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 pilot-scale batches for the 3, 4.5 and 6 mg strengths and 3 production-scale batches of the 1.5 mg strength. Process validation for full-scale batches of the 3, 4.5 and 6 mg strengths will be performed post authorisation.

Control of excipients

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

Quality control of drug product

The product specification includes tests for appearance, identification, water content, disintegration, dissolution, average weight, uniformity of dosage units, assay, related substances and microbiological quality. The shelf-life requirements are not identical to the release requirements in respect to water content, dissolution and average weight. The proposed specification is acceptable..The analytical methods have been adequately described and validated. Batch analytical data have been provided on 3 pilot-scale batches for the 3, 4.5 and 6 mg strengths and 3 full-scale batches for the 1.5 mg strength, demonstrating compliance with the proposed release specification.

Stability of drug product

Stability data on the product has been provided 3 pilot-scale batches for the 3, 4.5 and 6 mg strengths and 3 full-scale batches of the 1.5 mg strength, stored at 25°C/60% RH (up to 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 transparent PVC/Al-blisters. At both conditions a decrease in assay and increase in water content is observed. At accelerated conditions also an increase in total impurities is seen, an increase in disintegration time and a slight decrease in dissolution percentage. All tested parameters remain within the specified limits. A photostability study was performed, no decrease in assay or increase in impurities is observed, the drug product is concluded to be photostable. The proposed shelf life of 24 months without additional storage requirements could be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The gelatine as part of the capsule structure is of animal origin. CEPs have been provided from the manufacturers. A statement for magnesium stearate has been presented, demonstrating that this excipient is from vegetable origin.

II.2 Non clinical aspects

These products are generic formulations of Exelon, 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 rivastigmine 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

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

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Ristidic 1.5 mg and 6.0 mg (ICN Polfa Rzeszow S.A, Poland) is compared with the pharmacokinetic profile of the reference products Exelon 1.5 mg and 60 mg (Novartis Europharm Ltd., marketed in the EU).

The choice of the reference products
In the bioequivalence studies, the 1.5 mg product from the French market is used and the 6 mg tablet was obtained from the Spanish market. As the reference product has been registered through the centralised procedure, it is identical across the EU.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – 1.5 mg capsules
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fed conditions in 36 healthy subjects (24 females/12 males), aged 31 ± 9 years. Each subject received a single dose (1.5 mg) of one of the 2 rivastigmine formulations. After a supervised overnight fast of at least 10 hours, and 30 minutes before drug administration, subjects were served a standard breakfast. The breakfast consisted of one individual cereal box of Kellogg's Corn Flakes (27 g), one sugar packet, one carton of 2% M.F. milk (200 ml), 2 slices of toasted white bread, one Petit Quebec cheese (individual package, 21 g), two pats of butter, and one box of orange juice (200 ml). Subjects were required to consume this breakfast completely prior to drug administration. The tablet was orally administered with 240 ml water and subsequently the subjects fasted for a period of at least 4 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, and 10.0 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
Thirty-two subjects completed the study and were included in pharmacokinetic and statistical analysis. There was one withdrawal before dosing; this subject was replaced. There were 4 drop-outs: 2 for personal reasons and 2 due to adverse events.

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

Treatment N=32	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5673.36 ± 3182.90	5777.62 ± 3208.86	2570.98 ± 1331.50	2.00 (0.33-3.67)	0.91 ± 0.15
Reference	5561.05 ± 3280.76	5652.45 ± 3296.56	2447.74 ± 1238.39	2.00 (1.00-3.33)	0.91 ± 0.16
***Ratio (90% CI)**	1.03 (0.98–1.09)	1.03 (0.98-1.09)	1.03 (0.96-1.11)	-	-
CV (%)	12.5	12.0	17.2	-	-

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ 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 rivastigmine under fed conditions, it can be concluded that Ristidic 1.5 mg and Exelon 1.5 mg hard capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

<u>Bioequivalence study II – 6 mg capsules</u>
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fed conditions in 36 healthy subjects (15 females/21 males), aged 31 ± 9 years. Each subject received a single dose (6 mg) of one of the 2 rivastigmine formulations. After a supervised overnight fast of at least 10 hours, subjects were served a standard breakfast. The breakfast consisted of Kellogg's Corn Flakes, sugar, 2% milk, slices of bread, light cheddar cheese, butter, strawberry jam and orange juice (250 ml). Subjects were required to consume this breakfast within 30 minutes prior to drug administration. The tablet was orally administered with 240 ml water and subsequently the subjects fasted for a period of at least 4 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.0, and 12.0 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
Twelve subjects did not complete the studies; 10 of these experienced adverse events and the other 2 withdrew for personal reasons. The remaining 24 subjects completed the study and were included in the analysis.

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

Treatment N=24	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	58568.12 ± 36179.10	59309.02 ± 36440.64	20293.78 ± 12234.23	2.00 (0.67-3.00)	1.34 ± 0.25
Reference	57966.72 ± 33129.24	58872.84 ± 33308.70	20359.67 ± 9717.83	2.00 (1.00-3.33)	1.38 ± 0.28
***Ratio (90% CI)**	98.60 (91.86-105.83)	98.28 (91.72-105.31)	95.61 (86.78-105.34)	-	-
CV (%)	14.30	13.95	19.67	-	-

$AUC_{0-\infty}$ 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 rivastigmine under fed conditions, it can be concluded that Ristidic 6.0 mg and Exelon 6 mg hard capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The fed conditions of the bioequivalence studies are justified as the product is according the SPC recommended to be taken with food, to improve bioavailability. The bioequivalence studies under fed conditions are therefore acceptable.

Extrapolation to different strengths
A biowaiver was granted for the 3 and 4.5 mg strengths, since the following conditions have been fulfilled:
- All strengths are manufactured by the same process and manufacturer.
- All strengths possess the same qualitative composition and the ratio between the excipients is considered similar (hard capsules have the same weight and the active substance comprises less than 5% of the total weight).
- All 4 strengths have similar dissolution profiles (all tested products release more than 85% in 15 min).
- Rivastigmine has linear pharmacokinetics up to 3 mg twice daily but is non-linear at higher doses. However, the BE studies have been performed with the lowest and the highest strenght, which is the most sensitive approach to detect differences in the rate and extent of absorption between formulations.

The results of the bioequivalence study performed with the 1.5 and 6 mg capsules therefore apply to the other strengths.

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/Pharmacovigilance

Rivastigmine was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of rivastigmine can be considered to be well established. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

For Exelon, a Risk Management Plan has been constituted in which several safety issues have been identified. The MAH committed to monitor and specifically report upon the following issues in the PSURs: gastro-intestinal symptoms (nausea, vomiting and diarrhoea); worsening of symptoms associated with Parkinson's disease; increased amylase, lipase and pancreatitis; cardiac arrhythmia; exacerbation of asthma and COPD; liver disorders including hepatitis; severe skin reactions (bullous reactions); cardiac disorders (myocardial infarction); haematuria; hypertension; cerebrovascular accidents; urinary tract obstruction; seizures (convulsions); gastrointestinal ulceration; and pulmonary infections.

The MAH will follow, where appropriate, the risk minimisation activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc. (see also post-approval commitments on page 9).

Product information

SPC

The SPC will follow and be kept in line with that of the innovator product.

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. A pilot test was first performed with 3 professionals, followed by two rounds with 10 participants each.

No weaknesses of the PIL were identified from the questions specifically addressing the key safety issues or from the open questions aiming to identify positive and negative impressions of the PIL (including lay-out). Nevertheless, the MAH proposed to replace "somnolence" by "drowsiness" in the section on driving and using machines. The proposal was considered acceptable.

The results of the user testing are acceptable according to the guideline on the readability, because the criterion "90% of literate adults are able to find the information requested within the package leaflet, of whom 90% can show that they understand it" is fulfilled.

In summary, the package leaflet is in line with the current readability requirements. The results show that the leaflet is easy to read and understandable. However, evaluation of the submitted mock-up showed that the lay-out of the leaflet needed to be amended, e.g. part of the text was arranged in a way that is not in agreement with the QRD-template. Therefore, the MAH has submitted an alternative proposal for the lay-out of the PIL. The MAH has submitted a document in which the proposed lay-out is compared with the lay-out of a leaflet that successfully passed a readability test. Furthermore a small test was performed with 5 participants that focused on the proposed lay-out. The MAH also confirmed that several other PILs with a similar lay-out but different content have successfully passed user consultation. The member states therefore consider that the readability of the proposed leaflet has been sufficiently demonstrated.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ristidic 1.5 mg, 3.0 mg, 4.5 and 6.5 mg capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Exelon hard capsules. Exelon 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 in the agreed templates and consistent with that of the reference product.

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 Ristidic 1.5 mg, 3.0 mg, 4.5 and 6.5 mg capsules, hard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 October 2009. Ristidic 1.5 mg, 3.0 mg, 4.5 and 6.5 mg capsules, hard is authorised in the Netherlands on 4 November 2009.

The MAH will follow the PSUR-cycle agreed for the innovator's product. The next data lock-point will therefore be 31 July 2010. The first PSUR will cover the period from .. to July 2010, after which te PSUR submission cycle will be 3 years.

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

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

Quality - medicinal product

- The MAH committed to continue stability studies of the submitted batches according to the stability protocol up to 60 months. In addition, the first three production scale batches of each strength of drug product will be tested for their stability under both long term and accelerated conditions. The results will be submitted and the shelf-life specifications will be reevaluated when updated stability data are available.

Pharmacovigilance

- The MAH committed to adhere to the PSUR cycle of the innovator.
- The MAH committed to monitor and specifically report upon several issues in the PSURs (see page 8).
- The MAH committed to follow the SPC of the innovator and to keep the SPC for its products in line with the innovator.
- The MAH committed to follow, where appropriate, the risk minimisation activities of the innovator, e.g. participate in DHPCs where needed, produce and distribute educational material for patients and physicians when applicable, etc.

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