CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rivastigmine DEMO 1.5/3/4.5/6 mg capsules
Demo SA Pharmaceutical Industry, Greece

rivastigmine (as 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/1512/001- 004/DC
Registration number in the Netherlands: RVG 103038-41

19 July 2010

Pharmacotherapeutic group:	anti-dementia drugs; anticholinesterases
ATC code:	N06DA03
Route of administration:	oral
Therapeutic indication:	mild to moderately severe Alzheimer's dementia; mild to moderately severe dementia in patients with idiopathic Parkinson's disease
Prescription status:	prescription only
Date of authorisation in NL:	20 April 2010
Concerned Member State:	Decentralised procedure with EL
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 Rivastigmine DEMO 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules, from Demo SA Pharmaceutical Industry. The date of authorisation was on 20 April 2010 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 products Exelon 1,5 mg, 3 mg, 4,5 mg, and 6 mg capules (EU License EU/1/98/066) which have been registered through a centralised procedure by Novartis Europharm Limited since 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 product is compared with the pharmacokinetic profile of reference products Exelon 1.5 mg and 6 mg capsules, registered in the Netherlands. 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 rivastigmine hydrogen tartrate, an established active substance not described in the European (Ph.Eur.*), or any other Pharmacopoeia. The active substance is a white to almost white powder and is soluble in methanol, ethanol, acetonitrile and water and partly soluble in acetone. 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.

Manufacture
For both drug substance manufacturers, the manufacturing process consists of three main reaction steps and a purification step. The starting materials and solvents have been described sufficiently. No metal catalysts are used. The active substance has been adequately characterized and the specifications that have been adopted for the starting material, solvents and reagents are acceptable.

Quality control of drug substance
The drug substance specification 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.

Stability of drug substance.
First manufacturer - stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (12 months) and 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 without any additional storage requirements is justified.
Second manufacturer - stability data on the active substance have been provided for 3 full-scale batches stored at 25°C/60% RH (18 months) and 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 30 months is justified when stored in the original container is justified.
The MAH has committed to continue long term testing for up to 3 years to cover the desired re-test period of 3 years.

** 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
Rivastigmine DEMO 1.5 are hard gelatin capsules, with a yellow coloured body and a yellow coloured cap. The cap is imprinted radially with "*R9VS*" above "*1.5*" in black ink.
Rivastigmine DEMO 3.0 are hard gelatin capsules, with a yellow coloured body and a orange coloured cap. The cap is imprinted radially with "*R9VS*" above "*3*" in black ink.
Rivastigmine DEMO 4.5 are hard gelatin capsules, with a red coloured body and a red coloured cap. The cap is imprinted radially with "*R9VS*" above "*4.5*" in black ink.
Rivastigmine DEMO 6.0 are hard gelatin capsules, with a yellow coloured body and a red coloured cap. The cap is imprinted radially with "*R9VS*" above "*6*" in black ink.

The excipients are:
Capsule contents - magnesium stearate (E572), hypromellose (E464), microcrystalline cellulose (E460), colloidal anhydrous silica (E551).
Capsule shell - gelatin (E441), yellow iron oxide (E172), titanium dioxide (E171).
Printing ink - shellac, propylene glycol, strong ammonia solution, potassium hydroxide, black iron oxide (E172).

The capsules are packaged in PVC/Aluminium blisters. The excipients and packaging are usual for this type of dosage form.

Except for the 4.5 and 6 mg strength, the composition of the capsules is not proportional.

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 are justified. The different strengths of the drug product show a similar dissolution profile in media of pH 1.2, 4.5 and 6.8. A fast dissolution of more than 85 % in 15 minutes is shown for all capsule strengths. For the clinical studies, rivastigmine 1.5 mg capsules, manufactured at Oman Pharmaceutical Products, were compared with the originator Exelon 1.5 mg capsules. The composition of the biobatch is similar to the final product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process mainly consists of the preparation of the primary granulate, preparation of the final blend and the encapsulation process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 production batches for both manufacturing sites.

Container closure system
No special compatibility studies were performed. During stability studies no interactions between packaging materials and product were observed.

Excipients
The excipients comply with the Ph.Eur. requirements or with the requirements of Directive 95/45/EC for quinoline yellow. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, uniformity of mass, identification, assay, impurities, efficacy of antimicrobial preservation and microbial contamination. Except for total impurities, the shelf-life requirements are identical to the release requirements. The requirements are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on three production batches, demonstrating compliance with the release specification.

Microbiological attributes
The drug product complies with the requirements of Ph.Eur. 5.1.4 monograph (category 3A) on *Microbiological Quality of Pharmaceutical Preparations*.

Stability tests on the finished product
Stability data on the product has been provided for 3 production batches stored at 25°C/60% 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 clear PVC/Al-blisters. No changes are seen under both storage conditions. The claimed shelf-life of 24 months without any special storage conditions is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation 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 a bioequivalence study in which the pharmacokinetic profile of the test product Rivastigmine DEMO 1.5 mg capsules (Demo SA Pharmaceutical Industry, Greece) is compared with the pharmacokinetic profile of the reference product Exelon 1.5 mg capsules (Novartis Pharma, the Netherlands.

Exelon tablets are registered via the centralised procedure and are therefore presumed to be identical in all member states of the EEA.

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

Bioequivalence study – 1.5 mg
A single centre, randomized, single dose, laboratory-blinded, two-period, two-sequence, crossover bioequivalence study was carried out under fed conditions in 34 healthy (17 male, 17 female) volunteers, mean age: 35 ± 11 years. After a supervised overnight fast of at least 10 hours, subjects received a standardized high-fat, high-calorie meal within 30 minutes before drug administration. Within 30 minutes after the start of breakfast, a single dose (1.5 mg) of the assigned formulation was orally administered with 240 ml of water. The meal comprised 240 mL of whole milk, 2 eggs fried in butter, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with 11 g of butter, and 2 strips of bacon. A standardized lunch was served afterwards approximately 4.75 hours after drug administration. Water was allowed *ad libitum* until 2 hours pre-dose and 2 hours after drug administration. Subjects were allowed to leave the clinical site after the 8-hour blood draw.
There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected predose and at 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 7 and 8 hours after administration of the products.
The analytical method is adequately 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
Thirty-two subjects completed both of the study periods and were included in analytical and statistical analysis. However, only 26 subjects were available for descriptive statistics of AUC∞ because the terminal phases of rivastigmine could not be adequately estimated for six subjects.
One subject was withdrawn before dosing of period 2 for safety reasons (abnormal ECG recordings). Another subject withdrew his consent before dosing of period 2 for personal reasons.

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

Treatment N = 32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml N=26	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3.896 ± 2.769	4.381 ± 3.066	1.492 ± 0.963	3.33 (0.67 – 6)	1.02
Reference	4.103 ± 3.268	4.393 ± 2.996	1.562 ± 1.099	3.00 (0.67 – 5)	---
***Ratio (90% CI)**	1.00 (0.92 -1.09)	1.00 (0.92 – 1.10)	0.98 (0.87 – 1.10)	---	---
CV (%)	19.9	19.2	27.3	---	---

$AUC_{0-\infty}$ 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

**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 hydrogen tartrate under fed conditions, it can be concluded that Rivastigmine DEMO 1.5 mg capsules and the Exelon 1.5 mg 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 results of the bioequivalence study with the 1.5 mg strength however could not be extrapolated to the 3 mg, 4,5 mg and 6 mg strengths, for the following reasons:

- Rivastigmine shows non-linear PK profile for doses higher than 3 mg. In addition, a biowaiver for the 3 mg strength is also not acceptable due to the non-similar ratio between excipients (cellulose microcrystalline/ hydroxypropyl methylcellulose) compared to 1.5 mg strength.
- The biowaiver to 4.5 mg and 6 mg strength is hampered by the non-linear PK profile of rivastigmine.

Therefore the applications for the 3 mg, 4.5 mg and 6 mg strength were not considered approvable. The MAH was asked to perform a bioequivalence study with the highest, and the most sensitive to detect differences, 6 mg strength. The biowaiver to 3 mg and 4.5 mg strengths can be in principle claimed based on bioequivalence with 6 mg strength. Single dose studies with 6 mg strength have been shown to be feasible for other applications in the EU. The BE study with the 6 mg strength is described hereafter.

Bioequivalence study – 6 mg

Test: Rivastigmine DEMO 1.5 mg capsules (Demo SA Pharmaceutical Industry, Greece)
Reference: Exelon 6 mg capsules (from German market)

A single centre, randomized, single dose, laboratory-blinded, two-period, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy (13 male, 15 female) subjects, of mean age 31 ± 8 years.
After a supervised overnight fast of at least 10 hours, subjects received a standardized normocaloric, meal within 30 minutes before drug administration. Within 30 minutes after the start of breakfast, a single dose (6 mg) of the assigned formulation was orally administered with 240 ml of water.The meal comprised 27g of cereal Kellog's Corn Flakes, a sugar packet, 200 mL of 2% M.F. milk, 2 slices of toasted white bread, 21g of Petit Quebec cheese, 2 pats of butter, and 200 mL of orange juice. A standardized lunch was served afterwards approximately 4.00 hours after drug administration. Water was allowed *ad libitum* all the time. Subjects were allowed to leave the clinical site after the 12 hour blood draw in each period.
There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected predose and at 0.333, 0.667, 1, 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, 10.00 and 12.00 hours after administration of the products.
The analytical method is adequately 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
Of the 28 healthy male and female subjects included in the study, 19 subjects completed both of the study periods and were included in analytical and statistical analysis. This is acceptable. There were 9 drop-outs in the study: seven subjects were withdrawn due to the vomiting within 6 hours after dosing in Period I. One subject withdrew his informed consent before dosing in Period II due to the safety reasons (fatigue, loss of appetite, dizziness). One subject withdrew his informed consent due to personal reasons. The large number of the subjects withdrawn from the study due to the safety reasons is not unexpected since administration of high doses of rivastigmine to the healthy subjects despite the co-medication is still associated with tolerance problems.

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

Treatment N = 19	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	59.17 ± 46.28	61.27 ± 50.04	17.88 ± 8.28	2.00 (1.00 – 3.67)	1.63 ± 0.64
Reference	56.96 ± 49.51	60.30 ± 58.34	17.42 ± 9.16	2.00 (1.00-4.50)	1.56 ± 0.54
***Ratio (90% CI)**	1.05 (0.96 – 1.15)	1.05 (0.96 -1.15)	1.04 (0.93 –1.16)	---	---
CV (%)	16.25	16.12	19.90	---	---

$AUC_{0-\infty}$ 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 AUC0-t, AUC0-∞ and Cmax 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 hydrogen tartrate under fed conditions, it can be concluded that Rivastigmine DEMO 6 mg capsules and the Exelon 6 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results

A biowaiver of the 3 and 4.5 mg strengths was claimed based on the bioequivalence study of the 6 mg strength which is considered acceptable since the conditions for the waiver are met in accordance with the current *Guideline on the Investigation of Bioequivalence*.

It was noted that for the 3 mg strength a small difference (1.5%) in microcrystalline cellulose content is used (ie ratio compared to 6 mg strength) to compensate for the lower amount of active substance. This small difference is however not expected to negatively affect the release of rivastigmine. This is supported by the *in vitro* dissolution profiles of the 3 mg and 6 mg capsules which are demonstrated to be similar.

In conclusion, all criteria for a biowaiver for the 3 and 4.5 mg strength are met.

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

For the innovator product Exelon, a RMP has been constituted which has been updated based on post-marketing safety information. The MAH has committed to follow the RMP of the innovator, where appropriate. The MAH has therefore committed to the following issues:

- the following issues will be monitored and specifically reported upon 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 SPC for the product will follow and be kept in line with that of the innovator.

The MAH has 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.

Product information

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. Before the user testing was started, some amendments to the PIL were proposed in order to improve readability. The MAH amended the PIL in line with this proposal before the start of the user testing.

After a pre-round with 2 participants, two cohorts of 10 participants were interviewed. Amendment of the PIL was not considered necessary after the pre-round and the first round with 10 participants. This was confirmed with the second round of 10 participants.

Diagnostic testing was performed. Questions (14 in total) were asked about all parts of the leaflet. Furthermore, four general questions have been formulated about the general impression of the PIL (positive/negative aspect, style).

The report is clear and of good quality, The results show that the package leaflet meets the criteria for readability as set in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rivastigmine DEMO 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules have a proven chemical-pharmaceutical quality and are a generic form of Exelon 1,5 mg, 3 mg, 4,5 mg, and 6 mg 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 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 Rivastigmine DEMO 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 July 2009. Rivastigmine DEMO 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules are authorised in the Netherlands on 20 April 2010.

The PSUR submission cycle should be aligned with the PSUR submissions of the innovator product Exelon with the first data lock point of 31 July 2010. Currently (at the time of writing), a 6-monthly PSUR cycle is applicable for the innovator product and depending on the content of these PSURs this may change in the future.

The date for the first renewal will be: 16 July 2014. The MAH has the possibility to apply for an early renewal should this be more convenient to align the renewal application with the PSUR submissions in the future.

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

Quality - active substance

- The MAH has committed to continue long term testing for up to 3 years to cover the desired retest period of 3 years.

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