CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Venlafaxine Krka 37.5 mg, prolonged release capsules, hard
Venlafaxine Krka 75 mg, prolonged release capsules, hard
Venlafaxine Krka 150 mg, prolonged release capsules, hard

KRKA, d.d. Novo mesto, Slovenia

venlafaxine hydrochloride

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/799/001-003/DC
Registration number in the Netherlands: RVG 33647, 33648, 33649

7 April 2008

Pharmacotherapeutic group:	psychoanaleptics, antidepressants, other antidepressants
ATC code:	N06AX16
Route of administration:	oral
Therapeutic indication:	treatment of major depressive episodes, short-term treatment of generalised anxiety disorder (according to DSM-IV), short-term treatment of social anxiety disorder/social phobia, treatment of panic disorder with or without agoraphobia
Prescription status:	prescription only
Date of authorisation in NL:	28 November 2007
Concerned Member States:	CZ, DE, DK, EE, ES, FI, LT, LV, NO, PL, PT, SE, 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 Venlafaxine Krka 37.5 mg, 75 mg, 150 mg prolonged release capsules, hard, from KRKA, d.d. Novo mesto, Slovenia. The products have been granted authorisation in The Netherlands on 28 November. The product is indicated for treatment of major depressive episodes, short-term treatment of generalised anxiety disorder (according to DSM-IV), short-term treatment of social anxiety disorder/social phobia and treatment of panic disorder with or without agoraphobia.

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

Venlafaxine is an antidepressant, which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants (e.g. SSRI). Venlafaxine is a racemate with two active enantiomers.
The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethyl-venlafaxine, are potent inhibitors of serotonin and noradrenalin reuptake. Venlafaxine inhibits also weakly dopamine uptake. Studies in animals show that tricyclic antidepressants may reduce β-adrenergic responsiveness following chronic administration. In contrast, venlafaxine and O-desmethyl-venlafaxine reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and O-desmethyl-venlafaxine are very similar with respect to their overall action on neurotransmitter reuptake.
Venlafaxine has virtually no affinity for rat brain muscarinic cholinergic, H1-histaminergic or α1-adrenergic receptors in vitro. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular side effects. Venlafaxine does not possess monoamine oxidase inhibitory activity.

This application concerns a generic application claiming essential similarity with the innovator product Efexor XR 37.5, 75 and 150 mg capsules, which have been registered in the Netherlands by Wyeth Pharmaceuticals B.V. since 1994 (Dutch MA-numbers RVG 20862, 20863 and 26661). In addition, reference is made to Efexor authorisations in the individual member states (reference product).

The marketing authorisation is granted in the Netherlands based on article 10(1) of Directive 2001/83/EC. In all concerned member states the legal basis for the 75 and 150 mg strengths is article 10(1). In CZ, EE, LT, LV, PL, PT, and SK the legal basis for the 37.5 mg strength is also article 10(1), whereas in DE, DK, ES, FI, NO, and SE the legal basis is article 10(3), a so called hybrid application. These deviations are made, because of the absence of the 37.5 mg strength for the innovator in the latter countries. However, since all strengths applied for are in agreement with the posology, all applications were deemed acceptable. The observed differences in legal base are allowed.

These type of applications refer 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 and hybrid 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 these kind of applications, 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 Trevilor retard 75 and 150 mg capsules, registered in Germany (Trevilor retard is the name for the German innovator product). A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture has no influence on efficacy and safety. These products can be used instead of their reference products.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged 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 and excipients
The active substance is venlafaxine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months without specific storage conditions. The MAH committed to submit the results of ongoing stability testing of the API (Active Pharmaceutical Ingredient) according to EP specification after termination of the stability testing or if significant changes occur.

All excipients comply with either the Ph.Eur. or USP* specifications. It is acceptable that the gelatine capsules itself comply with in-house specifications.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition
Venlafaxine Krka 37.5, 75, and 150 mg prolonged release capsules, hard, contain as active ingredient venlafaxine hydrochloride (42.43, 84.85 and 169.70 mg) corresponding to 37.5, 75.00 and 150.00 mg of venlafaxine, respectively. The capsules are filled with white to almost white coloured pellets. The three strenghts are dose-proportional.

Venlafaxine Krka 37.5 mg prolonged release capsules have a brownish pink body and white cap.
Venlafaxine Krka 75 mg prolonged release capsules have a light pink capsule.
Venlafaxine Krka 150 mg prolonged release capsules have an orange-brown capsule.

The excipients are:
Capsule contents: sugar spheres (sucrose and maize starch), hydroxypropylcellulose (E463), povidone K-30 (E1210), ethylcellulose, dibutyl sebacate, talc (E553B).
Capsule shell: gelatine, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172) – the latter only in 75 mg and 150 mg capsules.

The capsules are packed in PVC/PVDC-Al blister pack or in a HDPE container.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients used are common in the manufacture of prolonged release capsules. The packaging materials are usual and suitable for the product at issue.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 commercial-scale batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for prolonged release capsules in the Ph.Eur. and includes tests for appearance, identity, uniformity of mass, the release rate of venlafaxine hydrochloride, loss on drying, residual solvents, degradation and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches for each strength in accordance with applicable European guidelines demonstrating the stability of the product over 18 months. On the basis of the submitted data, a shelf life of 2 years without further storage conditions has been granted.

Specific measures concerning the prevention of the transmisssion of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM has been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of Efexor XR, 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 venlafaxine hydrochloride 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

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

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Efexor XR 37.5, 75, and 150 mg capsules marketed by Wyeth Pharmaceuticals.

For this generic application, the MAH has submitted three bioequivalence studies. The bioequivalence studies were carried out with the 150 mg strength (single-dose study under fasted and fed conditions) and with the 75 mg strength (multiple-dose study). The fed condition is in accordance with the recommended administration posology of the drug as stated in the SPC. Intake with food is recommended to prevent adverse events and not for pharmacokinetic reasons, as the pharmacokinetics of venlafaxine is not altered due to concomitant food intake.
The reference products used in the bioequivalence studies were Trevilor retard 75 mg capsules and Trevilor retard 150 mg capsules from Wyeth Pharma GmbH, Germany. Trevilor is the name of the innovator product in Germany.

Study 1 Single-dose study under fasted conditions
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 19-27 years. All subjects completed the study and were eligible for pharmacokinetic evaluation. Each subject had 2 dosing periods, separated by a washout period of 7 days. The capsules were administered with 240 ml water after an overnight fast. Venlafaxine Krka 150 mg prolonged release capsules, hard, KRKA d.d. Novo mesto,

Slovenia, was compared to the reference product Trevilor 150 mg controlled release capsules, Wyeth Pharma GmbH, Germany.

Table 1. Pharmacokinetic parameters of venlafaxine (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) following a single-dose administration under fasted conditions

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1376 ± 863	1423 ± 881	84 ± 30	5.75 ± 0.79	10.1 ± 2.8
Reference	1419 ± 892	1456 ± 894	89 ± 39	6.08 ± 0.97	10.1 ± 2.1
***Ratio (90% CI)**	0.99 (0.93-1.04)	0.99 (0.94-1.04)	0.96 (0.90-1.02)	--	--
CV (%)	10.5	9.5	12.3	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters of O-desmethylvenlafaxine (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) following single-dose administration under fasted conditions

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	4919 ± 1448	5038 ± 1456	175 ± 45	9.46 ± 1.84	11.2 ± 2.1
Reference	5019 ± 1304	5134 ± 1284	187 ± 46	9.08 ± 1.41	10.9 ± 1.8
***Ratio (90% CI)**	0.97 (0.93-1.01)	0.97 (0.93-1.00)	0.93 (0.89-0.96)	--	--
CV (%)	7.1	7.1	7.1	--	--

$AUC_{0-\infty}$ 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*

Although venlafaxine as well as its metabolite O-desmethylvenlafaxine were evaluated, data on the parent drug venlafaxine will prevail for assessment of bioequivalence. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for venlafaxine are within the bioequivalence acceptance range of 0.80-1.25. The same holds for O-desmethylvenlafaxine. The statistical analysis of the pharmacokinetic data was adequate. A low coefficient of variation is observed, which is a known property of the drug.

Study 2 Single-dose study under fed conditions

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 24 healthy male subjects, aged 20-27 years. One subject did not start the study, and 2 subjects were withdrawn due to vomiting. Twenty-one subjects completed the study and were eligible for pharmacokinetic evaluation. Each subject had 2 dosing periods, separated by a washout period of 14 days. The capsules were administered with 240 ml water, 30 minutes after intake of a high-fat breakfast. Venlafaxine Krka 150 mg prolonged release capsules, hard, KRKA d.d. Novo mesto, Slovenia, was compared to the reference product Trevilor 150 mg controlled release capsules, Wyeth

Pharma GmbH, Germany. Also in this study both venlafaxine and O-desmethylvenlafaxine were determined.

Table 3. Pharmacokinetic parameters of venlafaxine (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) following a single-dose administration under fed conditions

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1966 ± 1667	2001 ± 1677	132 ± 67	5.52 ± 0.87	8.6 ± 4.8
Reference	1967 ± 1673	2008 ± 1677	116 ± 55	5.1 ± 0.4	11.1 ± 10.1
***Ratio (90% CI)**	1.00 (0.94-1.06)	1.00 (0.94-1.05)	1.13 (0.90-1.02)	--	--
CV (%)	10.0	9.5	10.5	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 4. Pharmacokinetic parameters of O-desmethylvenlafaxine (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) following a single-dose administration under fed conditions

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	5419 ± 1844	5493 ± 1839	212 ± 84	10.05 ± 3.09	10.1 ± 1.5
Reference	5053 ± 1613	5139 ± 1630	185 ± 67	9.95 ± 3.11	10.8 ± 2.0
***Ratio (90% CI)**	1.07 (1.01-1.12)	1.06 (1.01-1.12)	1.14 (1.08-1.19)	--	--
CV (%)	9.5	9.5	7.8	--	--

$AUC_{0-\infty}$ 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 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for both venlafaxine and O-desmethylvenlafaxine are within the bioequivalence acceptance range of 0.80-1.25. The statistical analysis of the pharmacokinetic data was adequate. A low coefficient of variation is observed.

Study 3 Multiple-dose study under fed conditions

A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 19-55 years. Each subject received a single dose daily for 5 consecutive days. The capsules were administered with 240 ml water after the intake of a standardised breakfast. For each subject there were 2 dosing periods, separated by a washout period of 7 days. Two subjects withdraw prior to drug administration. As per protocol, data from 22 subjects were used for pharmacokinetic and statistical analysis. This is considered acceptable and is in accordance with the recommended administration posology of the drug as stated in the SPC. Venlafaxine Krka 75 mg prolonged release capsules, hard, KRKA d.d. Novo mesto, Slovenia, was compared to the

reference product Trevilor 75 mg controlled release capsules, Wyeth Pharma GmbH, Germany. Also in this study both venlafaxine and O-desmethylvenlafaxine were determined.

Table 5. Pharmacokinetic parameters of venlafaxine (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) following a multiple-dose administration under fed conditions

Treatment	AUC_{τ} ng.h/ml	$C_{max,ss}$ ng/ml	$C_{min,ss}$ ng/ml	t_{max} h	FI %
Test	1017 ± 870	74 ± 43	19.0 ± 27.3	5.64 ± 1.09	157 ± 40
Reference	943 ± 845	64 ± 40	21.6 ± 29.6	5.50 ± 1.30	134 ± 38
***Ratio (90% CI)**	1.09 (1.04-1.15)	1.17 (1.10-1.246)	0.83 (0.76-0.91)	--	1.19 (1.12-1.24)
CV (%)	9.5	11.4	15.9	--	9.0

$AUC_{0-\infty}$ 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*

Table 6. Pharmacokinetic parameters of O-desmethylvenlafaxine (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) following a multiple-dose administration under fed conditions

Treatment	AUC_{τ} ng.h/ml	$C_{max,ss}$ ng/ml	$C_{min,ss}$ ng/ml	t_{max} h	FI %
Test	2390 ± 793	129 ± 42	65 ± 24	7.64 ± 1.68	64 ± 21
Reference	2289 ± 762	120 ± 40	67 ± 23	7.73 ± 1.52	55 ± 18
***Ratio (90% CI)**	1.05 (1.02-1.08)	1.08 (1.04-1.12)	0.97 (0.92-1.01)	--	1.17 (1.08-1.248)
CV (%)	5.5	7.1	8.4	--	13.1

$AUC_{0-\infty}$ 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 the main variables AUC_{τ} and $C_{max.ss}$ for both venlafaxine and O-desmethylvenlafaxine were inside the normal range of acceptability (0.80 - 1.25). This was also the case for the FI of the parent and the $C_{min,ss}$ and FI(%) for the metabolite. The wider CI for the C_{min}, 0.76-0.91, is acceptable. This is not considered to be critical towards the quality of the product. The statistical analysis of the pharmacokinetic was adequate.

Based on the pharmacokinetic parameters of venlafaxine and O-desmethylvenlafaxine in the single-dose studies, it can be concluded that test Venlafaxine Krka 150 mg capsule and reference Trevilor retard 150 mg capsule are bioequivalent with respect to rate and extent of absorption under fasted and fed conditions, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. In addition, the pharmacokinetic parameters of venlafaxine and O-desmethylvenlafaxine in the multiple-dose study also show bioequivalence with respect to rate and extent of absorption for test Venlafaxine Krka 75 mg capsule and reference Trevilor retard 75 mg capsule.

The Venlafaxine Krka 37.5, 75 and 150 mg prolonged release capsules are dose proportional and are filled with the same pellets. The pharmacokinetics of the active substance are linear in the therapeutic range. The results of the bioequivalence studies performed therefore apply to all mg strengths.

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 concerned member states.

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

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

Venlafaxine hydrochloride was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of venlafaxine hydrochloride 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.

Readability Test

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed. The test process involved two rounds.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Venlafaxine Krka 37.5, 75 and 150 mg prolonged relase capsules, hard, are generic forms of Efexor XR 37.5 mg, 75 mg and 150 mg controlled release capsules. Efexor XR 37.5, 75 and 150 mg controlled release capsules are well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the European guidance documents. The SPC is consistent with that of the reference product.

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.

The Board followed the advice of the assessors. The member states have granted a marketing authorisation for Venlafaxine Krka 37.5, 75 and 150 mg prolonged release capsules, hard.

There was no discussion in the CMD(h). Agreement between concerned member states was reached during a written procedure.

The PSUR submission cycle is 3 years. The 1st PSUR will cover the period from February 2007 until February 2010.

The date for the first renewal will be 6 February 2012.

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

Quality

- The MAH committed to submit the results of ongoing stability testing of the API (Active Pharmaceutical Ingredient) according to EP specification after termination of the stability testing or if significant changes occur.

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
PL	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 procedure	Approval/ non approval	Assessment report attached