CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Levetiracetam Pfizer 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets
Pfizer B.V., the Netherlands

levetiracetam

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/2161/001-004/DC
Registration number in the Netherlands: RVG 108577-108580

1 May 2012

Pharmacotherapeutic group:	other antiepileptics
ATC code:	N03AX14
Route of administration:	oral
Therapeutic indication:	as monotherapy partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy; as adjunctive therapy in partial onset seizures with or without secondary generalisation in patients > 1 month of age with epilepsy; as adjunctive therapy in myoclonic seizures in patients > 12 years with Juvenile Myoclonic Epilepsy; as adjunctive therapy in primary generalised tonic-clonic seizures in patients > 12 years with Idiopathic Generalised Epilepsy.
Prescription status:	prescription only
Date of authorisation in NL:	19 October 2011
Concerned Member States:	Decentralised procedure with AT, BE, BG, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, LU, NO, PL, PT, RO, SE, SI, SK, UK
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 Levetiracetam Pfizer 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets from Pfizer B.V. The date of authorisation was on 19 October 2011 in the Netherlands.

The product is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

The product is indicated as adjunctive therapy:

- in the treatment of partial onset seizures with or without secondary generalisation in adults, children and infants from 1 month of age with epilepsy.
- in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- in the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

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

The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances.
The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Keppra 250, 500, 750 and 1000 mg film-coated tablets which have been registered in the EEA by UCB Pharma through centralised procedure EU/1/00/146/001-029 since 29 September 2000 (original product).

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 support the application, the MAH submitted an argumentation for not performing a bioequivalence study for this application. 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. A bioequivalence study demonstrates that the generic product can be used instead of its reference product. For this generic application, the MAH argued that levetiracetam is a highly soluble and permeable drug with a wide therapeutic index, and thus can be classified as a Biopharmaceutical Classification System (BCS) class I drug substance. Therefore, the MAH applied for a BCS-based biowaiver for the bioequivalence study, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Further argumentation is discussed in section II.3 'Clinical aspects'.

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 levetiracetam, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Levetiracetam is a white to an off-white crystalline powder. The drug substance is very soluble in water, soluble in acetonitrile and practically insoluble in hexane. Levetiracetam contains an asymmetric carbon leading to two enantiomers. Levetiracetam is manufactured as the (S)-enantiomer. There is an absence of polymorphism in the active substance.

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/EMA 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
A description is presented of the synthetic route of levetiracetam, including structures, reagents/solvents and a reaction scheme of the process. Thereafter, levetiracetam is purified by crystallization. Adequate specifications are applied for the starting materials.

Quality control of drug substance
Ph. Eur. specifications are applied, plus additional requirements for a residual substance, microbiological quality (according to Ph. Eur.5.1.4 Non-aqueous preparations for oral use), particle size and bulk density. The drug substance specifications for levetiracetam based on Ph. Eur. plus additional in-house specifications are considered acceptable. For the in-house analytical methods, adequate (cross) validation data have been provided. All batch analysis results, including those from validation studies, are satisfactory meeting the set requirements.

Stability of drug substance
Three batches of the drug substance have been stored for 4 years at 25°C/65% RH and 6 months at 40°C/75% RH. All results easily met the set (Ph. Eur.) requirements, and there were no observed trends. Based on the provided data, the claimed re-test period of 4 years without specific storage condition can be granted.

** 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
Levetiracetam Pfizer, formulated as a film-coated tablet, contains 250 mg, 500 mg, 750 mg or 1000 mg levetiracetam. The tablets are described as blue (250 mg), yellow (500 mg), orange (750 mg) or white (1000 mg) coloured, oval shaped and biconvex, debossed with a deep break line separating 'E' and respectively '10', '11', '12' or '13' on one side, and plain on the other side. The tablets of all strengths can be divided into equal halves.
Levetiracetam Pfizer film-coated tablets are packed in PVC/PE/PVdC/Al blister packs or HDPE bottles with a polypropylene cap pack.

The excipients are:
Core – maize starch, silica colloidal anhydrous (E551), povidone (K-30) (E1201), talc (E553b), magnesium stearate (E470b)
Coating – hypromellose 3cp and 6cp (E464) (250 mg, 500 mg and 750 mg), hypromellose 5cp (E464) (1000 mg), titanium dioxide (E171), macrogol 4000 (250 mg, 500 mg and 750 mg), macrogol 400 (1000 mg), indigo carmine aluminium lake (E132) (250 mg and 750 mg), iron oxide yellow (E 172) (500 mg), sunset yellow aluminium lake (E110) (750 mg), iron oxide red (E 172) (750 mg)

The composition of the different strengths is dose proportional and the coating materials differ only in colouring agents.

Pharmaceutical development
The aim was to develop 250 mg, 500 mg, 750 mg and 1000 mg strengths of levetiracetam tablets as dose proportional formulations, with the same ratio between the amounts of active substance and excipients for all the strengths. With the finalised formulation, comparative dissolution studies with the innovator product (Keppra), comparative assay and impurities studies have been done.
The proposed product and the innovator product comprise different excipients, however, both formulations use well-established excipients in known amounts. In all comparative dissolution tests, the rate of drug release of the proposed product is rapid (≥ 85% in 15 min) and complete in 15 minutes, and the drug release profile is comparable with that of the corresponding innovator products. During manufacturing process development, various parameters of the production steps and coating parameters were further optimized. The development of the dissolution method has been adequately described.

Breakability studies have been performed. All tablets complied with the uniformity of mass of subdivided parts since all individual masses are within the acceptable limits of 85-115%.

Manufacturing process
An adequate description of the manufacturing process has been provided and a flow diagram is presented. The manufacturing process comprises straightforward steps like pre-sifting, dry mixing, wet granulation, drying, re-sifting, pre-lubrication mixing, lubrication, compression, film-coating, and packing.
Adequate in-process controls are applied during the several stages. The manufacturing process has been adequately validated according to relevant European guidelines. For the maximum scale size, adequate validation protocols have been submitted. Process validation data on the product has been presented for two batches. The MAH committed to perform validation studies post approval on the first three commercial batches.

Control of excipients
The excipients meet the requirements of the corresponding Ph. Eur. monographs. For the colorant used in the four mixtures, appropriate in-house requirements have been set, based on long term experience of the supplier.

Quality control of drug product
Process validation data on the product has been presented for appearance, thickness, identification, identification of colourants, average mass, water content, uniformity of dosage units, dissolution, HPLC assay, subdivision of tablets, and microbiological purity. In general, adequate specifications are proposed. For each tablet strength, results of two analysed batches have been provided. In view of the fully dose-proportional formulations, the total number of batch data is considered to be sufficient.

Stability of drug product
The MAH claims a shelf life of 3 years for all strengths without specific storage conditions in Alu-PVC/PE/PVdC blisters or in HDPE containers. For two batches per tablet strength, long-term and accelerated stability data are available. All results met the set requirements, including the tight dissolution requirement of NLT 85% after 15 min and the breakability results. Herewith the claimed shelf life of 3 years in the two packs without specific storage conditions can be granted.
The MAH provided in-use stability results for the HDPE tablet container on two batches of both 250 mg and 1000 mg tablets. In-use study data up to 12 months are available, wherein the HDPE container was subjected to daily simulation. Results from in-use stability studies demonstrated that all the quality

parameters were satisfactory, showing no significant changes. Therefore, the product does not require a separate in-use shelf-life after first opening of the HDPE container pack.

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. Magnesium stearate is of vegetable origin.

II.2 Non clinical aspects

This product is a generic formulation of Keppra, 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 levetiracetam 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

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

For this generic application, the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS-based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). The argumentation submitted by the MAH included various arguments as justification, including high solubility of levetiracetam drug substance, high permeability of levetiracetam drug substance, the almost complete absorption (> 95%) and rapid dissolution of levetiracetam tablets. In addition, the proposed biowaiver was demonstrated to be justifiable according to the criteria in Annex III of the Guideline on the Investigation of Bioequivalence.

A BCS (class I)-based biowaiver is applicable for an immediate release drug product if:

- the drug substance has been proven to exhibit high solubility and complete absorption; and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements; and
- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

Risk of therapeutic failure or adverse drug reactions
The MAH argued that levetiracetam cannot be considered a drug with narrow therapeutic index, based on argumentation concerning the safety profile, plasma monitoring, the dose-response relationship and paediatric information.

Safety profile and overdose
Levetiracetam is considered a well-tolerated anti-epileptic medication (Fix *et al.* 2002, in Vigevano 2005). The most frequent side effects are somnolence and asthenia. Both reactions are strictly dose dependent. In a systematic analysis of the literature on the tolerability of the various new antiepileptic drugs and of vagal stimulation, Cramer *et al.* (2001) (in Vigevano, 2005) concluded that levetiracetam had the best profile both for effectiveness and tolerability. The tolerability of levetiracetam is maintained over the long term and could extend to paediatric and elderly patients as well as those with learning disabilities (Arroyo *et al.* 2003). Overdose has been reported to be associated with somnolence, agitation, aggression, depressed consciousness, respiratory depression, and coma (Grünewald 2005). Recovery is rapid with appropriate supportive care. Levetiracetam has a wider safety margin in animal models compared with

other AEDs, inducing only minor behavioural alterations in normal and kindled rats (Klitgaard *et al.* 1998 (in Muralidharan *et al.* 2006) and having no negative impact on cognitive function in these animals (Lamberty *et al.* 2000 (in Muralidharan *et al.* (2006)), unlike classic antiepileptic drugs (Lamberty *et al.* 2000, in Arroyo *et al.* 2003).

The need for plasma monitoring and dose-response relationship:
The clinical value of plasma concentration measurements has not been established for levetiracetam, since the relationship between levetiracetam plasma concentrations and clinical effect has not been ascertained. However, data reflective of clinical settings are beginning to accumulate and there is suggestion that the plasma concentration of levetiracetam is related to the efficacy of the drug and that therapeutic monitoring of levetiracetam may be useful (Folland *et al.* 2002, Mushtaq *et al.* 2002, Lindholm, 2002, in Patsalos 2004). Meencke *et al.* (2006) assessed the dose–response relationships for levetiracetam efficacy by evaluating the pooled data from three trials including adults with refractory partial epilepsy. The combined analysis showed an increasing effect with increasing dose. This finding is consistent with an extensive review of levetiracetam safety results that also showed no relationship between levetiracetam doses of 1000–3000 mg/day and incidence of adverse events (Harden 2001, French 2001 (in Meencke *et al.* 2006)). The highest known dose of levetiracetam received in a clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events in the few known cases of overdose in clinical trials.

Pediatrics
The administration of a single dose (20 mg/kg administered as a 10% oral solution) to paediatric epilepsy patients aged 1 month to under 4 years of age was well tolerated (Glauser *et al.* 2007). An open-label, retrospective study of 52 consecutive paediatric patients (8 months to 16 years) treated with levetiracetam indicates at least partial efficacy in a variety of paediatric epilepsy syndromes. Tolerability was favourable, even at doses far exceeding 40 mg/kg/day (Koukkari *et al.* 2004).

Pharmacokinetic properties
In MAH demonstrated the high permeability and linearity of the kinetics of levetiracetam. The drug substance is rapidly and almost completely absorbed (> 95%) following oral administration; absorption is independent of dose, and extent of absorption is not affected by food. Levetiracetam exhibits linear pharmacokinetics over the dosage range of 500 to 5000 mg (Coupez *et al.* 2003).
A study of Ramael *et al.* (2005) (in Ramael *et al.* 2006) showed that an injectable formulation of levetiracetam administered IV (1,500 mg infused over 15 min) is bioequivalent with 1500 mg given as three 500 mg oral tablets and is well tolerated in healthy subjects (9 male, 9 female).
In multiple dose-ranging studies, levetiracetam has been observed to exhibit predictable, linear and dose-proportional steady-state pharmacokinetics, with steady-state concentrations occurring within 2 days of initiation of administration. More recently, two studies have reported that levetiracetam dose and blood concentrations are linearly related (Trinka *et al.* 2002, Perucca *et al.* 2003 (in Patsalos *et al.* 2004)). Single dose pharmacokinetics in healthy Asian male subjects were studied by Zhao *et al.* (2007) and both C_{max} and AUCs were dose-proportional over the range of 500–1500 mg. The pharmacokinetic data obtained in these Asian subjects were similar to the historical data from a matched group of Caucasian subjects.
Levetiracetam exhibits simple pharmacokinetics in children (aged 4 to 12 years), with rapid absorption and dose-proportional kinetics (Fountain *et al.* 2007) (in Glauser *et al.* 2007)) paediatric pharmacokinetic trials found levetiracetam's pharmacokinetics to be similar to those reported for adults except for more rapid drug clearance necessitating a higher dose in children on a mg/kg basis.

Solubility
Levetiracetam can be considered a highly soluble compound. The maximum dose for levetiracetam is 1500 mg. A solution of one dose of 1500 mg in 250 ml of water will lead to a concentration of 6 g/l. Solubility of levetiracetam is 1040 g/l and therefore the active substance can be considered highly water soluble. The solubility of levetiracetam is independent of pH.

BSC classification
Levetiracetam is highly water soluble and highly permeable. These characteristics of the substance justify the classification of levetiracetam as a Class 1 substance according to the Biopharmaceutical Classification System (BCS). Class 1 substances are generally suitable for a biowaiver. Generally the

risks of an inappropriate biowaiver decision should be more critically reviewed for products containing BCS class III than for BCS class I drug substances (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks).

Excipients
There are some differences in the qualitative composition of excipients between the generic product and the innovator Keppra. However, only well-established excipients are used in usual amounts. Therefore, these differences are acceptable.

***In vitro* dissolution**
Dissolution of Levetiracetam Pfizer 250 mg, 500 mg, 750 mg and 1000 mg tablets were evaluated in various media. It was observed that the drug release was rapid in all the media evaluated (i.e. dissolved greater than 85% at 15 minutes in water, 0.1N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer) and the dissolution profiles are similar to the reference product.

Conclusion
Levetiracetam is a highly soluble and permeable drug and thus it can be classified as a BCS class I drug substance. Comparative dissolution profiles show that levetiracetam test and reference products exhibit immediate release dissolution characteristics at all three pH levels with more than 85% of drug dissolved within 15 min, for all tablet strengths. There are some differences in the qualitative composition of excipients between the generic product and the innovator Keppra. However, only well-established excipients are used in usual amounts and none of the excipients can be classified as 'active' excipients. Therefore, these differences are acceptable. It can be concluded that the requirements for a biowaiver as mentioned in the Guideline on the Investigation of Bioequivalence are fully met. Levetiracetam is not a drug with a narrow therapeutic index. It is considered that a BCS-based biowaiver is fully justified.

Risk management plan
Levetiracetam was first approved in 2000, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of levetiracetam 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.

Pharmacovigilance
The innovator product Keppra currently has a one-year PSUR cycle. Therefore, the MAH agreed to follow a one-year PSUR cycle upon approval for Levetiracetam Pfizer. The MAH also committed to submitting 6-monthly specific safety reports for children < 4 years old in between yearly PSURs, which is in correspondence with the agreed PSUR cycle of the innovator product.

The MAH committed to continue to monitor the following events: abnormal behaviour, blood dyscrasias, seizure worsening, long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children and safety in patients with different epilepsy syndromes younger than 12 months. In addition, the impact of levetiracetam on the teeth in children of this age group should be carefully monitored in post marketing.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the centralised reference product Keppra (EMEA/H/C/000277) except for the product specific particulars.

Readability test

No user testing of the PIL of Levetiracetam Pfizer 250 mg, 500 mg, 750 mg and 1000 mg has been performed. The final package leaflet mock up has used the established Pfizer 'house-style'. A bridging statement has been submitted with reference to the PIL of Doxorubicin solution for injection (assessed with a readability test and approved), which has a similar layout and design. Product specific information in this latter PIL deviates from the information in the PIL of the current product. However, the content of the PIL of Levetiracetam Pfizer is similar to the PIL of Keppra, which has been successfully user-tested. Therefore, the absence of a readability test is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Levetiracetam Pfizer 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Keppra 250, 500, 750 and 1000 mg film-coated tablets. Keppra is a well-known medicinal product with an established favourable efficacy and safety profile.

For this generic application, the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS (class I)-based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98). The argumentation included information on the high solubility and high permeability of levetiracetam drug substance, almost complete absorption and the rapid dissolution of levetiracetam tablets. In addition, the proposed biowaiver was justified according to the criteria in Annex III of the Guideline on the Investigation of Bioequivalence. The BCS-based biowaiver is fully justified and accepted.

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 and are in agreement.

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 Levetiracetam Pfizer 250 mg, 500 mg, 750 mg and 1000 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 September 2011. The product was authorised in the Netherlands on 19 October 2011.

Six-monthly specific safety reports for children < 4 years old should be submitted conform the data lock point for the innovator product.

The date for the first renewal will be: 31 July 2016.

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

<u>Quality - medicinal product</u>

- The MAH committed to complete method validation/method transfer activity at the testing sites prior to the EU batch release of commercial batches.

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List of abbreviations

AED	Antiepileptic drug
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BCS	Biopharmaceutical Classification System
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
EEA	European Economic Area
EU	European Union
HPLC	High-performance liquid chromatography
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