CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ropinirol Glenmark 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg film-coated tablets
Glenmark Generics [Europe] ltd, United Kingdom

ropinirole (as 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/1599/001-005/DC
Registration number in the Netherlands: RVG 103720-103723, 103725

12 May 2010

Pharmacotherapeutic group:	anti-parkinson drugs, dopamine agonists
ATC code:	N04BC04
Route of administration:	oral
Therapeutic indication:	Parkinson's disease; 0.25/0.5/1/2 mg only - symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome
Prescription status:	prescription only
Date of authorisation in NL:	16 February 2010
Concerned Member States:	Decentralised procedure with AT, BE, DE, DK, EL, ES, FI, FR, IE, IT, NO, PT, SE, 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 from Glenmark Generics [Europe] ltd. The date of authorisation was on 16 February 2010 in the Netherlands.

The product is indicated for treatment of Parkinson's disease under the following conditions:
- initial treatment as monotherapy, in order to delay the introduction of levodopa.
- in combination with levodopa, over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur ("end of dose" or "on-off" type fluctuations).

The 0.25 mg, 0.5 mg, 1 mg and 2 mg products only are also indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

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

Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.
Ropinirole alleviates the dopamine deficiency which characterises Parkinson's disease by stimulating striatal dopamine receptors. Ropinirole acts also in the hypothalamus and pituitary to inhibit the secretion of prolactin.
Moderate to severe idiopathic Restless Legs Syndrome is typically represented by patients who suffer with insomnia or severe discomfort in the limbs.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Requip 0.25/0.5/1/2/5 mg film-coated tablets (indication Parkinson's disease) and Adartrel 0.25/0.5/1/2 mg film-coated tablets (indication restless legs syndrome) by GlaxoSmithKline. Requip was first authorised in France on 8 July 1996. In the Netherlands, Requip has been registered since 2 December 1996 by mutual recognition procedure FR/H/111/001-005 (NL license RVG 20761-20765).
Adartrel 0.25/0.5/1/2 mg film-coated tablets has been registered in the Netherlands through MRP FR/H/258/001-004 since 26 April 2006 (NL license RVG 31670-31673). In addition, reference is made to Requip and Adartrel authorisations in the individual member states (reference product). Requip and Adartrel belong to the same global marketing authorisation.

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 mg product is compared with the pharmacokinetic profile of the reference product Requip 1 mg film-coated tablets, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for 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 ropinirole hydrochloride, an established active substance, however not described in the European, British or US Pharmacopoeia (Ph.Eur.*). The drug substance is a white to pale greenish yellow powder, which is freely soluble in water, soluble in methanol and very slightly soluble in ethanol. Crystalline form II is used.

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 synthesis processes, starting materials, solvents and reagents have been included in the description. The drug is being formed in a 9 step process. The manufacturing process has been adequately described. No class one solvents are used in the manufacturing process. The active substance has been adequately characterized.

Quality control of drug substance
The drug substance specifications have been established using in-house and Ph.Eur. methods. Stability indicating properties of the HPLC method for assay have been shown. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches. The MAH committed to reconsider the limits for the impurities in the drug substance, once more data of production-scale batches become available.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 25°C/60% RH (18 months) and at 40°C/75% RH (6 months). The batches were stored in the commecial packaging. Results of the accelerated and long term storage conditions showed a slight increase (up to 3 months) as well as a slight decrease (after 3 months) in the total impurities. Results remained within the limits and no other specific trends were noted. The claimed retest period of 24 months could therefore be granted; no special storage conditions are required.
The MAH committed to submit stability data covering the whole re-test period (24 months) when available.

** 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
Ropinirol Glenmark 0.25 mg is a white to off-white, circular, bevelled edged, biconvex film-coated tablet with '253' debossed on one side and 'G' on the other side.
Ropinirol Glenmark 0.5 mg is a pale yellow to yellow, circular, bevelled edged, biconvex film-coated tablet with '254' debossed on one side and 'G' on the other side.

Ropinirol Glenmark 1 mg is a pale green to green, circular, bevelled edged, biconvex film-coated tablet with '255' debossed on one side and 'G' on the other side.
Ropinirol Glenmark 2 mg is a pale pink to pink, circular, bevelled edged, biconvex film-coated tablet with '256' debossed on one side and 'G' on the other side.
Ropinirol Glenmark 5 mg is a blue, circular, bevelled edged, biconvex film-coated tablet with '257' debossed on one side and 'G' on the other side.

The film-coated tablets are packed in plain Aluminium/Aluminium blisters, white, opaque triplex (PVC/PE/Aclar)/Aluminium blisters and white opaque HDPE bottles with polypropylene child-resistant closure.

The excipients are:
Tablet core - anhydrous lactose, lactose monohydrate, microcrystalline cellulose (E460), anhydrous citric acid (E330), croscarmellose sodium (E468), magnesium stearate (E572).
Film-coating - hypromellose (E464), titanium dioxide (E171), macrogol 400, talc (E553b), and Iron oxide yellow (0.5 and 1 mg), Indigo carmine aluminium lake (0.5, 1 and 5 mg), Iron oxide red (0.5 and 2 mg), Iron oxide black (1 mg) or Brilliant blue FCF Aluminium Lake (5 mg).

The core tablets have the same composition except for the amount of active substance which is compensated by the amount of the diluent lactose anhydrous. The excipients and their quantities used are common in immediate release products, so no specific risks with respect to safety are expected.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to create a film-coated tablet which could be considered bioequivalent to the innovator product Requip/Adartel. Comparative dissolution profiles were provided. The choices of the packaging and manufacturing process are justified. The test and reference products used in the bioequivalence studies are acceptable from chemical point of view.

Manufacturing process
The tablets are manufactured by means of a 12 step process, including preparation of base granules and the final manufacturing of the film-coated tablets by sifting, blending, compression, coating and packing.
The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques, but is considered to be a non-standard process (API<2%). Process validation data on the product has been presented three production-scale batches of each strength.

Control of excipients
The excipients comply with the specifications of the Ph.Eur., except for the Opadry coating material. For the Opadry coating material an internal specifications by the supplier is given. The substances used in the coating are listed in the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of ropinirole and Opadry colour, average weight, disintegration time, dissolution test, uniformity of dosage units (content uniformity), related substances, assay, water content and microbiological quality. The release and end of shelf life specifications are identical except for related substances and assay. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided. The MAH committed to perform the following for the commercial batches:

- Blister Packs: Complete re-testing after packaging
- Bottle Packs: Re-testing for description and microbiological quality only and transcribe the results of the remaining tests from the complete analysis of the bulk tablets.

Stability of drug product
Stability data on the product has been provided for three production scaled batches of the each strength stored at 25°C/60%RH (24 months), 30°C/65%RH (24 months) and 40°C/75%RH (6 months). The

batches were stored in aluminium-aluminium blisters, Triplex-aluminium blisters, 60 cc or 300 cc HDPE bottles with a child-resistance closure. The bulk pack was stored at 25°C/60%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline.
An increase in degradation products was seen at accelerated conditions; one specified impurity fell outside its specification. Storage at long term and intermediate conditions also showed an increase in degradation products, although within specification except for one batch of the 0.25 mg. Photostability studies were performed, in accordance with the note for guidance on stability testing, as part of the forced degradations studies. Photolytic degradation was not noted in the assay not in the related substances. The claimed shelf life of 24 months for the commercial packing was justified for the 0.5 mg, 1 mg, 2 mg and 5 mg products. For the 0.25 mg a shelf life of 21 months is justified. The claimed storage condition *store below 30°C* is justified, and the product should be protected from moisture. The claimed shelf life of 6 months for the bulk pack is justified, the storage condition *store below 25°C* is justified. The in-use shelf life for the product packed in bottles for 84 days has been justified. It is therefore not considered necessary to assign an in-use shelf life for the product packed in the HDPE bottle.
The MAH committed to perform stability studies on three industrial-size batches and annual stability monitoring.

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 Requip, 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 ropinirole 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

Ropinirole 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 Ropinirol Glenmark 1 mg (Glenmark Generics ltd, UK) is compared with the pharmacokinetic profile of the reference product Requip 1 mg tablets (GSK, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I - 1 mg, fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male South Asian subjects. Each subject received a single dose (1 mg) of one of the 2 ropinirole hydrochloride formulations. The tablet was orally administered with 240 ml water under fasted conditions. Meals were served 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 20, 24 and 36 hours after administration of the products.

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

Results
One subject was withdrawn as he tested positive for alcohol breath analyzer test during chek-in of period II and 4 other subjects did not check in for period II. Six subjects experienced emesis before two times median $t_{max.}$ Twenty-five subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	18.30 ± 5.99	18.67 ± 5.99	2.09 ± 0.48	3.00 (0.67-5.00)	5.04 ± 0.96
Reference	17.15 ± 6.63	17.53 ± 6.67	2.05 ± 0.65	2.50 (0.83-5.00)	4.88 ± 0.99
***Ratio (90% CI)**	1.08 (1.02 -1.15)	1.08 (1.02-1.14)	1.04 (0.97-1.11)	-	-
CV (%)	12.24	12.14	13.83	-	-

$AUC_{0-\infty}$ 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 ropinirole under fasted conditions, it can be concluded that Ropinirol Glenmark 1 mg and Requip 1 mg tabletsare 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 - 1 mg, fed conditions</u>
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 42 healthy male subjects. Each subject received a single dose (1 mg) of one of the 2 ropinirole hydrochloride formulations. After an overnight supervised fast of at least 10 hours, subjects were given a high calorie, high fat breakfast exactly 30 minutes prior to dosing. The tablet was orally administered with 240 ml water. Water was permitted *ad libitum* until 1 hour before dosing and again 1 hour after dosing. The subjects received lunch at 4 h, snacks at 8 h and dinner 12 h after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.333, 1.667, 2, 2.333, 2.667, 3, 3.33, 3.667, 4, 4.333, 4.667, 5, 6, 8, 10, 12, 16, 20, 24 and 36 hours after administration of the products.

Analytical/statistical methods

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

Results
One subject was withdrawn due to an adverse event (acid peptic disease) in period I, one subject did not check in for period II and one subject withdrew consent in period II. Two subjects experienced emesis before two times median $t_{max.}$ The remaining 37 subjects were included in the pharmacokinetic analysis.

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

Treatment N=37	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	16.93 ± 7.22	17.43 ± 7.37	1.91 ± 0.86	3.67 (0.50-6.00)	4.77 ± 0.94
Reference	16.02 ± 6.91	16.44 ± 7.03	1.71 ± 0.60	3.67 (1.00-8.00)	4.73 ± 0.93
***Ratio (90% CI)**	1.06 (1.01-1.11)	1.06 (1.01-1.11)	1.09 (0.99-1.20)	-	-
CV (%)	12.57	12.08	25.05	-	-

$AUC_{0-\infty}$ 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 ropinirole under fed conditions, it can be concluded that Ropinirol Glenmark 1 mg and Requip 1 mg tabletsare bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Food effect
According to the SPC, the product may be taken with food to improve gastrointestinal tolerance. Bioequivalence studies under both fasted and fed conditions are therefore needed.

Extrapolation to different strengths
Ropinirol Glenmark tablets contain less than 5% of active substance. The ratio between amounts of different core excipients for different strengths is similar, except from lactose anhydrous (diluent). This deviation is acceptable according to a draft 'Guideline on The Investigation of Bioequivalence' which states that in case the preparation contains less than 5% of the active substance, the amounts of a filler can be changed to account for the change in amount of active substance, provided that the bioequivalence study has been conducted with the highest dose using strength. The bioequivalence study was performed with 1 mg tablet. However, the choice of the used strength has been justified based on safety grounds of healthy volunteers, therefore this deviation is considered acceptable.
The biowaiver for the additional strengths is justified with dissolution data of all concerned strengths (0.25, 0.5, 1, 2 and 5 mg tablets) at all three pH levels. These data demonstrate that the dissolution is fast with more than 85% of the drug product dissolved within 15 min. The results of the bioequivalence study performed with the 1 mg tablet therefore apply to the other strengths.

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

Ropinirole was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ropinirole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. 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 system

The MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market. The MAH has committed to include the responses provided during the DCP in the Pharmacovigilance system before marketing of the product.
Therefore the RMS considers that the Pharmacovigilance system as described by the MAH, including the responses provided during the procedure, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Product information

SPC

The SPCs are in accordance with the currently approved SPCs for Adartrel and Requip. There are separate SPCs for the 5 mg and for the other 4 strengths.

Readability test

The performance of a user testing was not considered necessary for the following reasons:

- reference was made to the recently finalised Decentralised Procedure DK/H/1209/001-007 for another generic ropinirole tablet. The proposed leaflet is nearly identical to the leaflet as approved for this procedure.
- reference was made to the PILs for Requip and Adartrel, which have been user tested. Although these texts are not completely in line with the current QRD format, they can be useful as a cross-reference for parts of the leaflet.
- reference was made to the user testing reports for other Glenmark products (for perindopril, glimepiride, topiramate and pramipexole containing tablets). The format and text headings of the leaflets tested for these products are equal to those used for the current leaflet for ropinirole.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ropinirol Glenmark 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Requip 0.25/0.5/1/2/5 mg and Adartrel 0.25/0.5/1/2 mg film-coated tablets. Requip and Adartrel are well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence under both fed and fasted conditions has been shown to be in compliance with the requirements of European guidance documents.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other ropinirole containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ropinirol Glenmark 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 18 November 2009. Ropinirol Glenmark 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg film-coated tablets were authorised in the Netherlands on 16 February 2010.

A European harmonised birth date has been allocated (8 July 1996) and subsequently the first data lock point for ropinirole is July 2010. The first PSUR will cover the period from November 2009 to July 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 8 March 2013.

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

<u>Quality - active substance</u>
- The MAH committed to submit stability data covering the whole re-test period (24 months) when available.

<u>Quality - medicinal product</u>
- The MAH committed to perform the following for the commercial batches:
    - Blister packs: Complete re-testing after packaging
    - Bottle packs: Re-testing for description and microbiological quality only and transcribe the results of the remaining tests from the complete analysis of the bulk tablets.
- The MAH committed to perform stability studies on three industrial-size batches and annual stability monitoring.

<u>Pharmacovigilance system</u>
- The MAH committed to implement the responses to questions raised during the procedure on the PhVS before the product is placed upon the market.

List of abbreviations

API	Active Pharmaceutical Ingredient
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