CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ramipril Accord 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules hard Accord Healthcare B.V., the Netherlands

ramipril

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/2445/001-004/DC
Registration number in the Netherlands: RVG 110566-110569

28 October 2013

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA05
Route of administration:	oral
Therapeutic indication:	hypertension; cardiovascular prevention; renal disease; symptomatic heart failure; secondary prevention after acute myocardial infarction
Prescription status:	prescription only
Date of authorisation in NL:	18 March 2013
Concerned Member States:	Decentralised procedure with IE, PL, PT, RO
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 Ramipril Accord 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules hard from Accord Healthcare B.V. The date of authorisation was on 18 March 2013 in the Netherlands.

The product is indicated for:

- Treatment of hypertension.
- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:
  - manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
  - diabetes with at least one cardiovascular risk factor.
- Treatment of renal disease:
  - incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria,
  - manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor.
  - manifest glomerular non diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day
- Treatment of symptomatic heart failure.
- Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction.

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

Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.
Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Tritace 1.25, 2.5, 5 and 10, capsules (NL License RVG 13294-13297), which have been registered by Sanofi-Aventis Netherlands B.V since 16 May 1990. In addition, reference is made to Tritace authorisations in the individual member states (reference 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 this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Triatec 5 mg capsules from Portugal and Tritace 10 mg capsules from 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 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 ramipril, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white, crystalline powder, which is sparingly soluble in water and freely soluble in methanol. Ramipril exhibits polymorphism; the anhydrous crystalline form is used.

The CEP procedure is used for both suppliers the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
Reference is made to the specification of the Ph.Eur. monograph on ramipril and the additional CEP requirements. An overall specification is set for the drug substance of both suppliers, with the exception of residual solvents. This is acceptable. The limits are in line with the monograph. Batch analysis data have been provided. Results show compliance with the drug substance specification as proposed.

Stability of drug substance
The re-test period of the drug substance from the first manufacturer is 60 months if stored under the stated conditions. For the second CEP holder, the re-test period of the drug substance is 36 months, if stored at the stated conditions.
Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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
Ramipril Accord 1.25 mg are yellow/white, size ‘4’ hard gelatin capsules, imprinted ‘R’ on cap and ‘1.25’ on body with black ink, containing white to off white powder.
Ramipril Accord 2.5 mg are orange/white size ‘4’ hard gelatin capsules, imprinted ‘R’ on cap & ‘2.5’ on body with black ink, containing white to off white powder.
Ramipril Accord 5 mg are scarlet/white size ‘4’ hard gelatin capsules, imprinted ‘R’ on cap & ‘5’ on body with black ink, containing white to off white powder.

Ramipril Accord 10 mg are blue/white, size '4' hard gelatin capsules, imprinted 'R' on cap & '10' on body with black ink, containing white to off white powder.

The capsules are packed in Aluminium-Aluminium blisters and PVC/PVdC-Aluminium blisters

The excipients are: capsule content - pregelatinised maize starch, capsule shell - gelatin, water, titanium dioxide (all strengths), iron oxide yellow (1.25/2.5 mg), erythrosine (2.5/5/10 mg), patent blue (5 mg), indigocarmine (10 mg) and iron oxide black (10 mg).

The 10 mg product contains over 5% active substance, the 1.25 mg contains less then 2% active substance. The ratio between amount of active substance and excipients is different but average weight remains the same for all the strengths. The difference due to content of active component in the various strengths is compensated by the excipient pregelatinized starch.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions are explained. It was aimed to create capsules which could be considered bioequivalent to the innovator product Tritace 5 and 10 mg capsules. Comparative dissolution profiles were provided, showing similarity between the innovator product and the reference product for both strengths. Choices of the packaging and manufacturing process are justified. The test and reference products used in the bioequivalence studies are acceptable from a chemical point of view.

Manufacturing process
The capsules are manufactured by means of sifting and blending of the active substance and excipient, encapsulation and packaging. The process is rather straightforward, although the lowest strength has to be considered a non-standard process (<2% active substance). The 2.5/5/10 mg product is manufactured using conventional manufacturing techniques in what is considered a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full-scale batches of the lower strength and two minimum-scale batches for the other strengths, which is acceptable in view of the Note for Guidance on Process Validation. An acceptable protocol for the validation of the production batches has been provided.

Control of excipients
The excipient complies with the specifications of the Ph.Eur. The capsule shell contains gelatin, CEPs for several different suppliers have been included. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, average weight of filled capsule, average net content, identification, loss on drying, disintegration time (only at release), dissolution, related substances, assay, content uniformity, and microbiological quality. 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 analysis data on three production-scale batches (1.25 mg) and three minimum-scale batch sizes (2.5/5/10 mg) have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three production-scale batches (1.25 mg) and two minimum-size batches (2.5/5/10 mg) stored at 25°C/60%RH (24 months for 1.25 mg; 36 months for 2.5 mg, 5 mg and 10 mg), 30°C/60%RH (12 months) and 40°C/75%RH (3-6 months). The batches were stored in aluminium-aluminium blister packs and PVdC-Aluminium blister packs. The conditions used in the stability studies are acceptable.
Photostability studies performed as per ICH guidance showed no changes in any of the parameters. It can be concluded that the product is photostable.
The claimed shelf-life of 18 months for the 1.25 mg product can be accepted. For the 2.5 mg product packaged in the PVdC-alu blister a shelf-life of 18 months can be accepted, while for the 2.5 mg packed in

the Alu-Alu blister a shelf-life of 2 years is acceptable. For the 5 and 10 mg capsules a shelf-life of 36 months is acceptable.

The claimed storage conditions stating that the capsules should not be stored above 25°C is justified. An additional condition 'Store in the original package to protect from moisture' is indicated, and is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The gelatin used in the capsule shell is manufactured from bovine source, i.e. cattle from a country where there have been no known incidences of BSE and TSE.

II.2 Non-clinical aspects

This product is a generic formulation of Tritace which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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 ramipril 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

Ramipril is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Ramipril Accord 10 mg (Accord Healthcare B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Tritace 10 mg capsules (Sanofi-aventis, the Netherlands).
However, in the Ramipril Accord formulation, the amount of filler, pregelatinised starch, is changed to compensate for the change in amount of active substance in the capsule range. In order to support the biowaiver request for the lower strengths, the 'Guideline on the Investigation of Bioequivalence' states that the amount of active substance must be less than 5% of the weight of the capsule content. For the 10 mg capsule this is not the case (i.e. 8.33%).
Therefore, the biowaver could not be accepted. With their response, the MAH submitted the results of a second study, in which Ramipril Accord 5 mg (Accord Healthcare B.V., the Netherlands) was compared to Triatec® 5 mg capsules (Sanofi-Aventis, Portugal).

The choice of the reference product
The choice of the reference products in the bioequivalence studies 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.

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.

Bioequivalence study I – 10 mg capsules
Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-44 years. Each subject received a single dose (10 mg) of one of the 2 ramipril formulations. The capsule was orally administered under fasted conditions. There were 2 dosing periods, separated by a washout period of 25 days.

Blood samples were collected pre-dose and at 0.2, 0.3, 0.5, 0.7, 0.8, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, 144, 192 and 240 hours after administration of the products. Samples were analyzed for both the parent and the metabolite compound.

The study design is acceptable. Sampling scheme is adequate to determine pharmacokinetic parameters and the washout period of 25 days is sufficient.

Results
The drop-outs were due to protocol deviations of not reporting for ambulatory blood sample drawing (4), non compliance to the study restrictions (1) or discontinuation of their own accord (3). Plasma samples of these 53 subjects were analyzed.

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

Treatment N=53	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	26.7 ± 10.1	27.6 ± 10.2	37.9 ± 18.8	0.5 (0.3 – 1.0)	1.8 ± 1.0
Reference	26.8 ± 9.5	27.7 ± 9.8	36.3 ± 16.0	0.5 (0.3 – 0.8)	1.9 ± 1.3
***Ratio (90% CI)**	0.99 (0.93 – 1.05)	0.99 (0.93 – 1.05)	1.02 (0.91 – 1.15)	--	--
CV (%)	19.0	18.7	40.2	--	--

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

**ln-transformed values*

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

Treatment N=53	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	471.8 ± 118.2	670.9 ± 174.8	35.4 ± 19.2	2.7 (1.3 – 6.0)	193.3 ± 50.1
Reference	466.4 ± 110.6	666.2 ± 182.6	33.5 ± 14.1	2.7 (1.7 – 5.0)	194.8 ± 53.4
***Ratio (90% CI)**	1.02 (0.99 – 1.05)	1.02 (0.98 – 1.05)	1.02 (0.95 – 1.09)	--	--
CV (%)	8.5	11.6	27.4	--	--

$AUC_{0-\infty}$	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 ramipril, supported by those of the active metabolite ramiprilat under fasted conditions, it can be concluded that Ramipril Accord 10 mg and Tritace 10 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.

There was a report for only 1 adverse event. One subject experienced fever after administration of the reference product, which was judged to be unrelated.

Bioequivalence study II – 5 mg capsules

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 18-44 years. Each subject received a single dose (5 mg) of one of the 2 ramipril formulations. The capsule was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.33, 3, 4, 5, 6, 8, 10 and 12 hours after administration of the products.

The study design is appropriate. The wash-out between periods was sufficient and the sampling schedule and frequency are suitable to adequately estimate the pharmacokinetic profile of ramipril.

Results

One subject discontinued the study on his own accord. Thus, a total of 55 subjects were included in pharmacokinetic and statistical analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ramipril under fasted conditions.

Treatment N=55	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	12.2 ± 6.1	12.5 ± 6.1	16.1 ± 9.5	0.67 (0.33 – 2.33)
Reference	11.3 ± 4.6	11.6 ± 4.7	14.5 ± 6.9	0.5 (0.33 – 1.67)
***Ratio (90% CI)**	1.04 (0.97-1.12)	1.04 (0.97-1.12)	1.07 (0.96-1.19)	--

$AUC_{0-\infty}$	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

**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 ramipril under fasted conditions, it can be concluded that Ramipril Accord 5 mg and Triatec® 5 mg capsulesare bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

No adverse events were reported during the course of the study.
Ramipril may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ramipril. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Biowaiver
The following criteria for a biowaiver are met:
- The 1.25/2.5/5 mg strengths are manufactured at the same site using a similar manufacturing process as that of 10 mg strength.
- Ramipril demonstrates linear pharmacokinetics over the therapeutic dose range.
- The qualitative composition of 1.25/ 2.5/ 5 mg formulation is the same as that of 10 mg formulation.
- The ratio between amount of active substance and excipients is different but average weight remains the same for all the strengths.
- The dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

The objection regarding the biowaiver for studies with the lower strengths is considered resolved. A bioequivalence study has been conducted using the highest strength (10 mg) as per guideline. Furthermore, a bioequivalence study with the lower strength (5 mg) has been conducted which provides the basis for biowaiver of the 1.25 and the 2.5 mg strengths as the active compound is lower than 5% of the capsule core weight for the 1.25, 2.5 and 5 mg 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
Ramipril was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ramipril 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.

Product information

SPC
The product information is in line with that of the innovator. The agreed Art.30 referral text (EMEA/H/A-30/970) for Tritace and associated names, the PhVWP wording for ACE inhibitors on pregnancy and lactation, as well as the Art.45 Paediatric Worksharing wording for ramipril (UK/W/0011/pdWS/001) have been implemented.

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. The test consisted of a pilot test with 2 participants, two rounds with 10 participants each. Sixteen questions were prepared to test for traceability, comprehensibility and applicability. The composition of the subject population is acceptable as far as age, gender and education are concerned.

The results of the first round of testing met the study objectives. Therefore, no amendments to the package leaflet were considered necessary. Also the results of the second round of testing met the study objectives.
In addition to the questionnaire, there were four questions at the end of the test in order to gain an opinion/feedback of the subject's interpretation of the full package leaflet. From the subject's answers to these questions and general comments, no adaptation of the package leaflet was deemed necessary.

There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ramipril Accord 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules hard have a proven chemical-pharmaceutical quality and are generic forms of Tritace 1.25, 2.5, 5 and 10 mg, capsules. Tritace 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 Ramipril Accord 1.25 mg, 2.5 mg, 5 mg and 10 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 February 2013. Ramipril Accord 1.25 mg, 2.5 mg, 5 mg and 10 mg, capsules hard were authorised in the Netherlands on 18 March 2013.

The date for the first renewal will be: 12 February 2018.

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

Quality - medicinal product

- The MAH committed to continue the stability studies to the end of the period shown for each batch and storage condition.
- The MAH committed to place the first production batch on long-term stability studies throughout the proposed shelf life.
- Comparative dissolution profiles for the 2.5/5/10 mg capsules will be established for a total of three product-scale batches before marketing of the product.

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