CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and 16 mg/12.5 mg, tablets Torrent Pharma GmbH, Germany

candesartan cilexetil/hydrochlorothiazide

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/2070/001-002/DC
Registration number in the Netherlands: RVG 107846-107847

22 September 2011

Pharmacotherapeutic group:	angiotensin II antagonists and diuretics
ATC code:	C09DA06
Route of administration:	oral
Therapeutic indication:	essential hypertension not sufficiently controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.
Prescription status:	prescription only
Date of authorisation in NL:	23 August 2011
Concerned Member States:	Decentralised procedure with DE, LT, 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 Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and 16 mg/12.5 mg, tablets from Torrent Pharma GmbH. The date of authorisation was on 23 August 2011 in the Netherlands.

The product is indicated for essential hypertension not sufficiently controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.

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

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension and other cardiovascular disorders. Furthermore, it is also significant in the pathogenesis of organ hypertrophy and end-organ damage. The most important physiological effects of angiotensin II, e.g. vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the receptor subtype 1 (AT_1).

Candesartan cilexetil is a prodrug which is rapidly converted into its active form, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin-II receptor antagonist with selectivity for the AT_1 receptor, with which it has a high binding affinity and from which its dissociation is slow. It has no agonist activity.

Hydrochlorothiazide inhibits active sodium reabsorption mainly in the distal renal tubules and promotes the excretion of sodium, chloride and water. Renal excretion of potassium and magnesium increases dose-dependently, whilst calcium is largely reabsorbed. Hydrochlorothiazide decreases plasma volume and extracellular fluid, reduces cardiac output and lowers the blood pressure. In long-term therapy, reduced peripheral resistance contributes to the reduction in blood pressure.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Atacand Plus 8 mg/12.5 mg and 16 mg/12.5 mg tablets (NL License RVG 23317 and 24995) which have been registered in the Netherlands by AstraZeneca through MRP SE/H/0162/001-002 since 9 February 1999 and 23 March 2000, respectively. In addition, reference is made to Atacand Plus 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: one in which the pharmacokinetic profile of the 8 mg/12.5 product is compared with the pharmacokinetic profile of the reference product Atacand Plus mite 8mg/12.5mg tablets, registered in Austria, and one study with the 16 mg/12.5 mg product versus Atacand Plus 16 mg/12.5 mg registered in Germany. 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 – candesartan cilexetil
Candesartan cilexetil is an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*). However, a draft Ph.Eur. monograph is published in Pharmeuropa Vol.22, No 1, January 2010. The drug substance is a white or off-white crystalline powder, which is insoluble in water, and soluble in methylene chloride and acetone. Candesartan cilexetil has one chiral centre and exists in three polymorphic forms (I, II and amorphous). The drug is manufactured as a racemic mixture as polymorphic form I.

The Active Substance Master File (ASMF) procedure is used for candesartan cilexetil. 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.

Manufacturing process
The manufacturing of candesartan cilexetil consists of eight steps. No class 1 organic solvents are used. Tin is used as metal catalyst in the manufacturing of one of the starting materials in the synthesis. Adequate specifications have been provided.

Quality control of drug substance
The drug substance specification is in line with the draft Ph.Eur. monograph, with additional requirements for heavy metals, azide content, XRD, residual solvents, particle size and microbial purity. The specification is acceptable in view of the route of synthesis and the various ICH guidelines.
Batch analytical data of three full-scale batches have been provided demonstrating compliance with the specification.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). All other parameters remain relatively stable at both conditions. Based on the provided stability data, a retest period of 24 months without specific storage conditions was 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.*

Active substance – hydrochlorothiazide
Hydrochlorothiazide (HCTZ) is an established active substance described in the Ph.Eur. It is a white to almost white crystalline powder, which is very slightly soluble in water, soluble in acetonre and sparingly soluble in ethanol

The CEP procedure is used for hydrochlorothiazide. 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 new 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
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specification of hydrochlorothiazide is in line with the requirements of the Ph.Eur. monograph for hydrochlorothiazide, with additional specifications for particle size and microbial purity.
Batch analytical data of the drug substance have been provided for three full-scale batches, demonstrating compliance with the specifications.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Medicinal Product

Composition
Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg is a white to off white, oval, biconvex, 9.5 x 4.5 mm, bevel edged uncoated tablet with breakline on both sides.
Candesartan cilexetil/Hydrochloorthiazide Torrent 16 mg/12.5 mg is a peach colored to light orange, oval, biconvex, 9.5 x 4.5 mm, bevel edged uncoated tablet with breakline on both sides.
Both tablets can be divided into equal halves.

The tablets are packed in Alu-Alu blisters or PVC/PVDC-Al blisters.

The excipients are: lactose monohydrate, maize starch, hypromellose 2910 (E464), calcium stearate, hydroxypropyl cellulose (E463), disodium edetate, microcrystalline cellulose (E460); additionally for 16/12.5 mg: ferric oxide red (E172), ferric oxide yellow (E172).

The 8 mg/12.5 mg differs from the 16 mg/12.5 mg tablets in lactose monohydrate percentage to make up for the differences in active substances and colourants.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the originator product, comparative dissolution studies and optimising the manufacturing process. Since for both strengths more than 85% was dissolved within 15 minutes, the dissolution profiles may be accepted as similar.
Bioequivalence studies were performed with both strengths. The batches used in the bioequivalence studies have the same composition and are manufactured in the same way as the future commercial batches. The subdivision of 8 mg/12.5mg and 16 mg/12.5mg tablets complies with the relevant Ph. Eur. monograph. The development has been described in sufficient detail.

Manufacturing process
The manufacturing process consists of sifting, dry mixing, wet granulation, drying, mixing, lubrication, compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches of each strength. Process validation for larger batch sizes will be performed post authorisation.

Control of excipients
The excipients comply with Ph. Eur., USP-NF or in-house requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of drug substances, identification of colorant, average mass, disintegration, water content, dissolution, uniformity of dosage units (content uniformity), related substances, assay, microbial limits and subdivision of tablets. The release and shelf-life limits are the same, except for water content and related substances. The release and shelf-limits are acceptable.
The analytical methods have been adequately described and validated, and are stability indicating (if required). Batch analytical data have been provided on two pilot-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two pilot-scale batches per strength stored at 25°C/60% RH (12 months), at 30°C/65% RH (12 months) and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu-Alu blisters and PVC/PVDC-Alu blisters. All results remained within specifications except for one impurity at accelerated conditions. Photostability data show that the drug product is not sensitive to light. Based on the provided stability information, a shelf life of 12 months was granted with the storage condition 'Do not store above 30°C'.

Several commitments have been made with regard to the drug product; these can be found on page 10 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only excipient of animal origin. A declaration is provided that the lactose is sourced from milk of healthy animals fit for human consumption in accordance with the guideline.

II.2 Non-clinical aspects

This product is a generic formulation of Atacand Plus, 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 candesartan cilexetil or hydrochlorothiazide 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

Candesartan cilexetil and hydrochlorothiazide are well-known active substances with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and 16 mg/12.5 mg tablets (Torrent Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference products Atacand Plus mite 8 mg/12.5 mg (AstraZeneca Österreich GmbH, Austria) and Atacand Plus 16 mg/12.5 m mg tablets (Astra Zeneca GmbH, Germany).

The choice of the reference product
The choice of the reference products 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 – 8 mg/12.5 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 19-42 years. Each subject received a single dose (8 mg/12.5 mg) of one of the 2 candesartan cilexetil/HCTZ formulations. The tablet was orally administered under fasted conditions with 200 ml water. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.3, 2.7, 3, 3.3, 3.7, 4.0, 4.3, 4.7, 5, 6, 7, 9, 12, 18, 24, 36 and 48 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

Two subjects withdrew consent the study because of personal reasons. The remaining 34 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 candesartan under fasted conditions.

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	733 ± 216	774 ± 218	76.9 ± 25.6	4.3 (2.3-6.0)	8.1 ± 2.3
Reference	676 ± 189	715 ± 191	70.0 ± 20.7	4.3 (2.0-6.0)	8.0 ± 2.1
***Ratio (90% CI)**	1.07 (0.99- 1.16)	--	1.09 (0.99-1.19)	**--**	**--**
CV (%)	19	--	23	--	--

$AUC_{0-\infty}$ 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 hydrochlorothiazide under fasted conditions.

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	468 ± 151	492 ± 151	66.6 ±18.8	2.17 (1.0-4.3)	9.2 ±1.3
Reference	498 ± 150	518 ± 155	72.0 ± 22.9	1.5 (1.0-4.0)	9.2 ±1.9
***Ratio (90% CI)**	0.93 (0.89-0.98)	--	0.93 (0.86-1.01)	--	--
CV (%)	13	--	20	--	--

$AUC_{0-\infty}$	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} 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 candesartan and HCTZ under fasted conditions, it can be concluded that Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and Atacan Plus mite 8 mg/12.5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – 16 mg/12.5 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 21-44 years. Each subject received a single dose (16 mg/12.5 mg) of one of the 2 candesartan cilexetil/HCTZ formulations. The tablet was orally administered under fasted conditions with 200 ml water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.3, 2.7, 3, 3.3, 3.7, 4, 4.3,4.7, 5, 6, 7, 9, 12, 18, 24, 36 and 48 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

Two subjects dropped out the study because of adverse events, one subject withdrew his consent. The remaining 33 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1491± 519	1548 ±532	138± 47	4.3 (2.0-6.0	9.1 ±2.4
Reference	1444 ± 493	1498 ± 503	133 ±48	4.3 (2.0-7.0)	9.1 ±2.2
***Ratio (90% CI)**	1.03 (0.94-1.13)	--	1.06 (0.92-1.22)	--	--
CV (%)	23	--	35	--	--

$AUC_{0-\infty}$	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 (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	564 ± 181	587 ± 185	76.6 ± 22.4	2.6 (1.0-4.3)	9.7 ± 1.5
Reference	586 ± 173	608 ± 174	80.6 ± 19.4	2.7 (1.0-4.7)	9.4 ± 1.2
***Ratio (90% CI)**	0.96 (0.90-1.02)	--	0.94 (0.88-1.01)	--	--
CV (%)	15	--	17	--	--

$AUC_{0-\infty}$ 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} 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 candesartan and HCTZ under fasted conditions, it can be concluded that Candesartan cilexetil/Hydrochloorthiazide Torrent 16 mg/12.5 mg and Atacan Plus 16 mg/12.5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Candesartan and HCTZ may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of candesartan or HCTZ. 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.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

The combination of candesartan and HCTZ has been authorised since 1999, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of candesartan/HCTZ 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. 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Atacand Plus (MRP SE/H/0162/001-002).

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, followed by two rounds with 10 participants each.
The developed questionnaire contained 19 questions specific to Candesartan cilexetil/HCTZ Torrent tablets and 3 specific to the format of the package leaflet. There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. Respondents were asked to give their answer in their own words.
A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PL, and 90% of all participants can show that they understand and can act upon it.
There were no changes made to the PL based on pilot testing. The data show all 19 questions met the success criteria in the first and second round. Based on quantitative and qualitative results, there were no revisions to the PL after the first and second round of testing. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and 16 mg/12.5 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Atacand Plus 8 mg/12.5 mg and 16 mg/12.5 mg. Atacand Plus 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 Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and 16 mg/12.5 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 8 July 2011. Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and 16 mg/12.5 mg were authorised in the Netherlands on 23 August 2011.

The date for the first renewal will be: 1 December 2015.

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

Quality - medicinal product

- The MAH committed to validate the first three consecutive commercial batches of both strengths for all proposed batch sizes.
- The MAH committed to place the first three batches of the largest batch size packed in each marketed container closure system (Alu-Alu and PVC/PVdC-Alu blister) on formal stability studies as per stability protocol.
- The MAH committed to revise the shelf life limit for impurities upon availability of complete stability data.

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