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M E B

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Kaliumlosartan HCS 25 mg, 50 mg and 100 mg film-coated tablets HCS bvba, Belgium

losartan (as potassium)

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/1611/001-003/MR
Registration number in the Netherlands: RVG 32426-8

6 August 2010

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA01
Route of administration:	oral
Therapeutic indication:	essential hypertension; renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment; chronic heart failure (in patients ≥ 60 years) when treatment with ACE inhibitors is not considered suitable due to incompatibility or contraindication; reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG.
Prescription status:	prescription only
Date of first authorisation in NL:	7 November 2007
Concerned Member States:	Mutual recognition procedure with AT, DE, and LV
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) for 50 and 100 mg, 10(3) for 25 mg

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 Kaliumlosartan HCS 25 mg, 50 mg and 100 mg film-coated tablets, from HCS bvba. The date of authorisation was on 7 November 2007 in the Netherlands.

The product is indicated for treatment of:

- essential hypertension.
- renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.
- reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG.

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

Losartan is a synthetic oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.
Losartan selectively blocks the AT1 receptor. In vitro and in vivo losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.
Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.
Both Losartan and its principal active metabolite have a far greater affinity for the AT1-receptor than for the AT2-receptor. The active metabolite is 10- to 40- times more active than Losartan on a weight for weight basis.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Cozaar 50 mg and 100 mg tablets, registered in the Netherlands (NL license RVG 17617 and 26791) by Merck Sharp & Dohme B.V. since 1995 and 2002, respectively. In addition, reference is made to Cozaar authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) (50 mg & 100 mg) and 10(3) (25 mg) of Directive 2001/83/EC. The application for the 25 mg strength is according to 10(3) hybrid application, because at the time of application, the 25 mg strength was not registered for the innovator product.

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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Lorzaar 50 mg and 100 mg tablets, both 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 generic medicinal products.

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 losartan, an established active substance described in the Ph.Eur.* The active substance is freely soluble in water and it shows polymorphism. Polymorphic form I is produced.

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.

Manufacture
The manufacture of losartan potassium consists of two main steps. The starting material and solvents have been aqequately described. Synthesis of the active substance does not involve Class 1 organic solvents or metal catalysts. The active substance was adequately characterised and acceptable specifications were adopted for the starting material, solvents, and reagents.

Quality control of drug substance
The drug substance specification is in accordance with the Ph.Eur. monograph on Losartan potassium with additional requirements for residual solvents and particle size distribution. The specification is acceptable in view of the route of synthesis and the various ICH guidelines.
Batch analytical data demonstrating compliance with the drug substance specification were provided for three consecutive production-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three pilot -and three full-scale batches stored at 25°C/60% RH (pilot batches: 60 months, full-scale batches: 48 months) and 40°C/75% RH (six months). The batches were adequately stored.
With the exception of an increase in water content of two of the full-scale batches at long term conditions and during photostability testing, no specific trends were observed. All tested parameters complied with the drug substance specification. The proposed re-test period of 48 months is justified. No special storage conditions are required.

* *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
The products are formulated as film-coated tablets containing either 25, 50, or 100 mg of losartan potassium and are packaged in Alu-PVC/PVDC blisters.

Kaliumlosartan HCS 25 mg are yellow, oval, light biconvex, scored, film-coated tablets. The tablet can be divided into equal halves.
Kaliumlosartan HCS 50 mg are white, round, light biconvex, bevel edged, scored, film-coated tablets. The tablet can be divided into equal halves.
Kaliumlosartan HCS 100 mg are white, oval, light biconvex, film-coated tablets.

The excipients are:
Tablet core: cellulose powdered, lactose monohydrate, pregelatinised maize starch, maize starch, microcrystalline cellulose, colloidal anhydrous silica (E551, magnesium stearate (E572).
Film-coating: hypromellose (E464), talc, propylene glycol, quinoline yellow (E104), titanium dioxide (E171), and quinoline yellow (E104) (only 25 mg strength).

All strenghts are fully dose proportional. The excipients and packaging are common for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Development focussed on a direct compression approach and a suitable dissolution method. The choices of the manufacturing process and the packaging are justified. The composition of the 50 and 100 mg pilot batches used in the bioequivalence studies is identical to the proposed commercial composition. German reference products were used.
Comparative dissolution profiles of all four strengths are provided showing comparable dissolution rates (> 80% in 20 minutes). Moreover, dissolution profiles of the generic and reference product batches used in the bioequivalence study were provided. The dissolution profiles were almost identical for the 50 mg strength and slightly different for the 100 mg strength with the generic product dissolving slightly faster than the reference product. The pharmaceutical development was adequately performed.

Excipients
With the exception of cellactose and quinoline yellow, the excipients comply with the Ph.Eur. Acceptable in-house specifications were laid down for cellactose and quinoline yellow.

Overages
20% overage in coating suspension is included due to losses during the coating process. This is usual.

Manufacturing process
The manufacturing process consists of direct compression followed by film-coating. The product is manufactured using conventional manufacturing techniques. The MAH has committed to perform process validation on three consecutive production-scale batches of each strength.

Quality control of drug product
The product specification includes tests for appearance, uniformity of mass, disintegration, hardness, water content, identification of Losartan, identification of titanium dioxide, identification of quinoline yellow, related substances, dissolution, assay, and microbiological purity. Release and shelf-life requirements differ with regard to water content and the level of total impurities. The drug product specifications are acceptable.
The analytical methods were adequately described and validated. Batch analytical data from the proposed production site were provided on three production-scale batches of each strength, demonstrating compliance with the release specification.

Breakability
Results of breakability testing for the 25 mg and 50 mg tablets were provided. The 100 mg tablets have no scores and do not have to be tested for breakability. The results comply with the test for uniformity of weight for tablet halves.

Stability tests on the finished product
Stability data on the product has been provided for three pilot-scale batches of the 50 mg, and of the 100 mg strength. Bracketing is applied for the 25 mg strength. The batches were stored at 25°C/60% RH (100 mg: 48 months, 50 mg: 60 months), 30°/65% RH (50 mg: 12 months), and 40°C/75% RH (six months). In addition, two production scale batches of the 25 mg strength and three of the 50 mg and 100 mg strength were added to the stability program. Data are available for 18 and 24 months at long term conditions, respectively, and for six months at accelerated conditions. Moreover, several batches of each strength were subjected to photostability testing. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/PVC-PVdC blisters.
The MAH has committed to place the first three production-scale batches of each strength on long term stability studies through the proposed shelf-life and on accelerated studies for six months. The results will be submitted when available.

Discussion of stability results
The level of related substances increased particularly at accelerated storage conditions. Therefore, the claimed shelf-lives of four years for the 25 and 100 mg strength and of five years for the 50 mg strength are acceptable but under the claimed storage conditions "*Store below 30°C*" and "*Store in the original package in order to protect from moisture*". The drug product is photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose contained in the excipient cellactose is the only excipient of animal origin. A statement of the manufacturer of cellactose declaring that the milk is sourced from healthy animals in the same condition as the milk collected for human consumption was provided.

II.2 Non clinical aspects

This product is a generic formulation of Cozaar, 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 losartan 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

Losartan 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 products Kaliumlosartan HCS 50 mg (HCS bvba, Belgium) and 100 mg film-coated tablets are compared with the pharmacokinetic profiles of the reference products Lorzaar 50 mg and 100 mg tablets (MSD, Germany).

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 (if applicable) in different member states.

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

Bioequivalence study 1 – 50 mg tablets
A single dose, randomised, open-label, two-way crossover bioequivalence study was carried out under fasted conditions in 26 healthy male volunteers, aged 18-45 years. Each subject received a single dose (50 mg) of one of the 2 losartan formulations. The tablet was orally administered with 200 ml water after a 10 hour fasting period. The first standard meal was served 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 and 36 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Losartan may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of losartan. 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.

Results
As one subject did not show up, twenty-five subjects completed all study periods and were eligible for pharmacokinetic analysis. The data of the main metabolite of losartan, losartan carboxy acid, were considered supportive.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of losartan 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	354 ± 158	375 ± 159	222 ± 146	0.8 (0.5 – 2)	1.72 ± 0.68
Reference	355 ± 177	376 ± 177	230 ± 123	0.9 (0.5 -2)	1.75 ± 0.36
***Ratio (90% CI)**	1.02 (0.94 – 1.10)	1.02 (0.95 – 1.08)	0.93 (0.80 – 1.07)	---	---
CV (%)	16	15	30	---	---

$AUC_{0-\infty}$	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*

Based on the data and calculations of the MAH for losartan all primary pharmacokinetic 90% confidence intervals were within the 0.80-1.25 borders for acceptation.

Bioequivalence study 2 – 100 mg tablets
A single dose, randomised, open-label, two-way crossover bioequivalence study was carried out under fasted conditions in 44 healthy male volunteers, aged 18-36 years. Each subject received a single dose (100 mg) of one of the 2 losartan formulations. The tablet was orally administered with 240 ml water after a 10 hour fasting period. The first standard meal was served 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected predose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 and 36 hours after administration of the products.
The analytical method is adequately validated and 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
Seven adverse events including headache, vertigo and orthostatic hypotension graded as mild were reported appearing in 5 subjects. The subjects recovered without sequelae. Both drugs were concluded to be safe and well tolerated in this trial. All 44 subjects completed all study periods and were eligible for pharmacokinetic analysis. The data of the main metabolite of losartan, losartan carboxy acid, were considered supportive.

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

Treatment N = 44	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	0.99 ± 0.38	1.06 ± 0.41	0.58 ± 0.32	1.1 (0.3–2.5)	2.86 ± 2.0
Reference	0.97 ± 0.36	1.02 ± 0.36	0.54 ± 0.29	1.2 (0.7–2.5)	2.58 ± 0.98
***Ratio (90% CI)**	1.02 (0.97 – 1.07)	1.03 (0.98 – 1.08)	1.07 (0.96 – 1.19)	---	---
CV (%)	13	13	31	---	---

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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for losdartan 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 losartan under fasted conditions, it can be concluded that Kaliumlosartan HCS 100 mg film-coated tablets and the Lorzaar 100 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.

Extrapolation of results
The tested 100 mg tablets are dose proportional with the 25 mg and 50 mg tablets. As the pharmacokinetics of losartan are linear the results of the 100 mg tablet can be extrapolated to the 25 mg and 50 mg strengths.

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

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 MAH chose to bridge the results of the user testing for Losartan /HCTZ (KrKa) tablets to Kaliumlosartan HCS tablets, registered by procedure CZ/H/101/01-02, based on the following grounds:

- Losartan / HCTZ contains a combination of losartan potassium 50 mg or 100 mg + hydrochlorothiazide 12.5 mg or 25 mg; Kaliumlosartan HCS contains losartan potassium only (25 mg, 50 mg or 100 mg).
- Losartan / HCTZ and Kaliumlosartan HCS are licensed for similar indications (hypertension), and therefore have the same target population.
- The method of taking the two medicines is the same.
- The precautions before taking the two medicines are similar.
- The expected side effects of the two medicines are similar.

The member states however were of the opinion that the approach of the MAH is not correct. As the content of the leaflet has been brought in line with the Art. 30 Referral procedure for losartan potassium containing tablets, a readability test for the wordings of the leaflet was not considered necessary. However, the MAH was asked to prove that the layout of their leaflet does not negatively influence the readability. See table 3 for the justification of the bridging report by comparison of layout, design and format of the PL between Kaliumlosartan HCS and Losartan/HCTZ.

Table 3. Justification of bridging report by comparison of layout, design, and format between PL for Kaliumlosartan HCS and Losartan/HCTZ.

Format, design and layout	<PRODUCT NAME> (losartan potassium)	<PRODUCT NAME> (losartan potassium/ hydrochlorothiazide)
PL Dimension	The dimension is the same in both PL's (360 mm x 123 mm).	The dimension is the same in both PL's (360 mm x 123 mm).
Font and font size	The font and font size is the same in both PL's.	The font and font size is the same in both PL's.
Headings and sub-headings	Headings and sub-headings have consistency of placement in both PLs.	Headings and sub-headings have consistency of placement in both PLs.
Use of colour and choice of colour	The colour used is the same in both PLs.	The colour used is the same in both PLs.
Style of writing and language used	Both bridged PLs are written and tested in English.	Both bridged PLs are written and tested in English.
Mock-up	The Mock-up for both PILs have vertical layout.	The Mock-up for both PILs have vertical layout.

The justification as provided by the MAH was accepted by the member states.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Kaliumlosartan HCS 25 mg, 50 mg and 100 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Cozaar 25 mg, 50 mg, and 100 mg tablets. Cozaar 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 and are in agreement with other losartan containing products. The recommendation of the pharmacovigilance working party regarding the use of Angiotensin II antagonists during pregnancy was implemented. The contra-indication "*lactation*" has been deleted and the lactation text in section 4.6 was updated.

The Board followed the advice of the assessors. Kaliumlosartan HCS 25 mg, 50 mg and 100 mg film-coated tablets were authorised in the Netherlands on 7 November 2007.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Kaliumlosartan HCS 25 mg, 50 mg and 100 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 19 June 2009.

The first PSUR will cover the period from June 2009 to September 2010, after which the PSUR submission cycle is 3 years

The date for the first renewal will be: 16 May 2014

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

<u>Quality - medicinal product</u>

- The MAH has committed to perform process validation on three consecutive production-scale batches of each strength.
- The HAH has committed to place the first three production scale batches of each strength on long term stability studies through the proposed shelf-life and on accelerated studies for six months. The results will be submitted when available.

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
Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules etc.) in a pack. Change outside the range of the currently approved pack sizes.	NL/H/1611/ 001-003/IB/ 001	IB	17-8-2009	16-9-2009	Approval	N
Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules etc.) in a pack. Change within the range of the currently approved pack sizes.	NL/H/1611/ 002-003/IA/ 002	IA	21-8-2009	4-9-2009	Approval	N
Change in the name and/or address of a manufacturer of the active substance where no Ph. Eur. Certificate for Suitability is available. New manufacturer (addition or replacement).	NL/H/1611/ 001-003/IB/ 003	IB	17-8-2009	16-9-2009	Approved	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/1611/ 001-003/IB/ 004	IB	18-8-2009	18-11-2009	Approved	N
Update of DMF.	NL/H/1611/ 001-003/II/ 005	II	3-8-2009	12-1-2010	Approved	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, including batch control/testing. Addition of a new batch and control release site.	NL/H/1611/ 001-003/IA/ 006	IA	18-8-2009	1-9-2009	Approved	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary and secondary packaging site. *Only for 25 mg strength:* Change in the batch size (including batch size ranges) of the finished product; .	NL/H/1611/ 001-003/IA 007/G	IA/G	8-3-2010	7-4-2010	Approved	N