

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Amoxicilline/Clavulaanzuur Pfizer 500/125 and 875 mg/125 mg
film-coated tablets
Pfizer B.V., the Netherlands**

amoxicillin (as trihydrate potassium clavulanate)

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/2241/001- 002/MR
Registration number in the Netherlands: RVG 107460-1**

**Date of first publication: 29 August 2011
Last revision: 21 March 2012**

Pharmacotherapeutic group:	combinations of penicillins, incl. beta-lactamase inhibitors
ATC code:	J01CR02
Route of administration:	oral
Therapeutic indication:	acute bacterial sinusitis (adequately diagnosed); acute otitis media; acute exacerbations of chronic bronchitis (adequately diagnosed); community acquired pneumonia; cystitis pyelonephritis; skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis; bone and joint infections, in particular osteomyelitis.
Prescription status:	prescription only
Date of first authorisation in NL:	28 September 2010
Concerned Member States:	Mutual recognition procedure with AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, HU, IE, IT, LT, LU, MT (not for 875 mg/125 mg strength), NO, PL, PT, RO, SE, SI, SK, and 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 Amoxicilline/Clavulaanzuur Pfizer 500/125 and 875 mg/125 mg film-coated tablets from Pfizer B.V. The date of authorisation was on 28 September 2010 in the Netherlands. The product is indicated for the treatment of the following infections in adults and children :

- Acute bacterial sinusitis (adequately diagnosed)
- Acute otitis media
- Acute exacerbations of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Cystitis
- Pyelonephritis
- Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.
- Bone and joint infections, in particular osteomyelitis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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

Amoxicillin

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Augmentin 500/125 mg and 875/125 mg filmcoated tablets (NL license RVG 09840 and 18553, respectively) which have been registered in the Netherlands by GlaxoSmithKline BV since 1983 (500 mg/ 125 mg) and 1996 (875 mg/ 125 mg). In addition, reference is made to Augmentin 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 study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Augmentin 500 mg/ 125 mg and 875 mg/ 125 mg tablets, registered in the UK and Germany, respectively. 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 substances

Amoxicillin trihydrate is an established active substance which is described in the Ph.Eur.*. Amoxicillin trihydrate is a white or almost white crystalline powder.

Potassium clavulanate is an established active substance which is described in the Ph.Eur.*. Potassium clavulanate is a white or almost white hydroscopic crystalline powder.

The CEP procedure is used for both active substances. 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture

For both substances this is covered by the CEP.

Quality control of drug substances

For both amoxicillin trihydrate and potassium clavulanate, Ph. Eur. specifications plus additional requirements from the involved CEPs are applicable.

Stability of drug substances

Amoxicillin trihydrate: on the CEP a re-test period of 2 years is stated when adequately stored.

Potassium clavulanate: on the CEP a re-test period of 48 months is stated when adequately stored.

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

Amoxicillin/Clavulanic acid Pfizer 500mg/125mg tablets are white, oval, film-coated tablets inscribed with 'A' on one side and '64' on the other side.

Amoxicillin/Clavulanic acid Pfizer 875mg/125mg tablets are white, capsule shaped, film-coated tablets inscribed with 'A' on one side and with a score line in between '6' and '5' on the other side. The score-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Both strengths are immediate-release tablets. The tablets can be distinguished by their dimensions.

The excipients are:

Tablet core: microcrystalline cellulose (E460), colloidal anhydrous silica, magnesium stearate (E470b), sodium starch glycolate (Type A)

Film-coating: hypromellose (E464), macrogol 400, titanium dioxide (E171)

The film-coated tablets are packed in Alu/Alu (polyamide/aluminium/PVC - aluminium foil) blister packs in a cardboard box.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development is mainly based on the qualitative composition of the originator product Augmentan tablets for both strengths (from GlaxoSmithKline, Germany). In the development the requirements of the monograph Co-Amoxiclav Tablets BP (British Pharmacopoeia) have been used as a guiding principle. The MAH concluded that the two originator strengths are not dose weight proportional, therefore this was also not intended for the proposed product. In the bioequivalence study, the batch size of the test bio-batch is of pilot-scale, the mentioned future manufacturing scale size is acceptable. The DE 875+125 mg reference product is acceptable in view of the composition of the NL originator product.

Dissolution studies

Comparing dissolution studies are performed for two batches of both strengths of the proposed product, including the 875+125 mg test bio-batch, using the DE reference bio-batch (875+125 mg) and UK originator bio-batch (500+125 mg). The proposed product shows slightly faster dissolution results in the 0-20 minutes trajectory in comparison with the originator products, this is not a problem.

Manufacturing process

The manufacturing process has been adequately described in sufficient detail, and adequate in-process controls have been listed. Pilot-scale batches have been validated, 2 batches per strength, and including the 875+125 mg test bio-batch. The finished product manufacturer commits in the dossier to validate a third batch (first commercial batch) at pilot-scale and the first three commercial batches at two specific scale sizes for the two strengths, respectively. This is acceptable.

Quality control of drug product

Adequate specifications are proposed for the drug product including the Ph. Eur. test on uniformity of dosage units. For two pilot-scale batches of each strength batch results have been provided. It is committed (see above) by the company to validate a third batch (first commercial batch) at pilot-scale and the first three commercial batches for the three strengths, which will render additional batch results.

Stability tests on the finished product

The stability results show that the proposed tablets are sufficiently stable. For both components slight to moderate assay decreases are observed, but are within the set requirements. Total impurities increase after 12 months at 30°C/70% RH, but remain within limits. Based on the stability data the claimed shelf-life of 2 years for both strengths without specific storage condition is justified.

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 Augmentin, 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 amoxicillin trihydrate or potassium clavulanate 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

Amoxicillin trihydrate and potassium clavulanate are 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 Amoxicilline/Clavulaanzuur Pfizer 500/125 and 875 mg/125 mg film-coated tablets Pfizer B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Augmentin 500/125 mg (GSK, UK) and 875/125 mg (GSK, Germany) film-coated tablets.

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.

The SPC states that the tablet should be taken with food to prevent gastro-intestinal AEs. There is no pharmacokinetic reason for intake with food. Therefore the study design (fed conditions) is considered acceptable.

Bioequivalence study with 875/125 mg tablets under fed conditions

An open-label, randomized, two-treatment, two sequence, two period, cross-over single-dose comparative oral bioequivalence study was carried out under fed conditions in 48 healthy Indian males, aged 19-40 years. Each subject received a single dose (875 mg amoxicillin trihydrate, 125 mg potassium clavulanate) of one of the 2 formulations in randomized order. Drugs were administered 30 minutes after a high fat meal of 955 KCal (approximately 60% of total calories consisted of fat). Tablets were taken with 240 ml of water. There was a washout interval of 8 days between the 2 dose administrations.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 5, 6, 7, 8, 10, and 12 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

One subject was dismissed for non-compliance (positive benzodiazepine test). Three subjects did not show up for Period II. Analysis of samples of 46 subjects who completed the study was performed. However the results of analysis for amoxicillin samples of subjects 1, 2, 38, 39 and 49 and those for clavulanic acid of subjects 1, 2 and 39 have not been reported. When these samples came up for analysis, they had already completed 3 freeze-thaw cycles. Stability of analyte beyond 3 freeze thaw samples could not be established during analytical method validation. Therefore, data from only 41 subjects for amoxicillin and 43 for clavulanic acid were reported.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of amoxicillin under fed conditions.

Treatment N = 41	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	50.7 \pm 8.9	51.4 \pm 9.0	15.7 \pm 3.5	2.3 (1 - 5)	1.5 \pm 0.3
Reference	48.8 \pm 8.6	49.4 \pm 8.5	15.3 \pm 3.4	2.3 (1.3 - 5)	1.5 \pm 0.3
*Ratio (90% CI)	1.03 (1.00 -1.07)	1.03 (1.00 -1.07)	1.02 (0.97 – 1.08)	---	---
CV (%)	8.3	8.2	15.1	---	---
AUC_{0-∞} 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					

**In-transformed values*

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

Treatment N = 43	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	4.0 \pm 2.3	4.6 \pm 2.5	1.9 \pm 1.1	2.3 (1.3 - 5)	1.0 \pm 0.2
Reference	3.7 \pm 1.6	4.3 \pm 1.7	1.7 \pm 0.8	2 (1.3 - 3)	1.0 \pm 0.2
*Ratio (90% CI)	1.01 (0.91 -1.13)	1.01 (0.88 - 1.15)	1.04 (0.92 -1.16)	---	---
CV (%)	30.9	30.4	32.4	---	---
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 amoxicillin and clavulanic acid under fed conditions, it can be concluded that Amoxicilline/Clavulaanzuur Pfizer 875 mg/125 mg film-coated tablets and the Augmentin 875/125 mg film-coated tablets. are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study with 500/125 mg tablets under fasted conditions

An open label, randomized, two-treatment, two-sequence, two-period, crossover, single dose comparative oral bioequivalence study was carried out under fed conditions in 50 (48+2 alternates) healthy male volunteers, aged 18-39 years. 42 of them were non smokers, and 8 subjects smoked 9 or less than 9

cigarettes a day. Each subject received a single dose (500 mg amoxicillin trihydrate, 125 mg potassium clavulanate) of one of the 2 formulations in randomized order after. Tablets were taken with 240 ml of water after an overnight fast. There was a washout interval of 3 days between the 2 dose administrations. Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 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.

The SPC states that the tablet should be taken with food to prevent gastro-intestinal AEs. There is no pharmacokinetic reason for intake with food. Therefore the study design (fasted conditions) is considered acceptable.

Results

One subject was withdrawn from study due to adverse events (fever) in the second period. Forty-nine subjects completed the study entirely, and as per protocol the first 48 subject were included in the analysis.

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

Treatment N = 48	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	24.80 \pm 5.36	25.37 \pm 5.43	8.21 \pm 2.29	2.0 (0.75 – 4.0)	1.16 \pm 0.19
Reference	26.44 \pm 6.04	26.92 \pm 6.06	8.78 \pm 2.68	2.0 (1.0 – 5.0)	1.15 \pm 0.18
*Ratio (90% CI)	0.95 (0.92 – 0.98)	0.94 (0.92 – 0.97)	0.94 (0.90 – 0.99)	---	---
CV (%)	8.1	7.9	14.9	---	---
AUC_{0-∞} 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					

**In-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{\max} (median, range)) of clavulananic acid under fasted conditions.

Treatment N = 48	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	6.40 \pm 2.52	6.62 \pm 2.52	2.63 \pm 0.98	1.25 (0.75 – 3.0)	1.10 \pm 0.15
Reference	6.72 \pm 2.41	6.96 \pm 2.41	2.71 \pm 0.96	1.5 (1.0 – 3.0)	1.13 \pm 0.19
*Ratio (90% CI)	0.93 (0.87 – 1.01)	0.93 (0.87 – 1.00)	0.96 (0.89 – 1.03)	---	---
CV (%)	22.1	20.8	22.8	---	---
AUC_{0-∞} 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					

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 amoxicillin and clavulananic acid under fasted conditions, it can be concluded that Amoxicilline/Clavulaanzuur Pfizer 500 mg/125 mg film-coated tablets and the Augmentin 500/125 mg film-coated tablets. are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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 amoxicillin trihydrate and potassium clavulanate was first approved in 1983, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amoxicillin trihydrate and potassium clavulanate 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 SPC of Amoxicillin/Clavulananic acid Pfizer is compared with the Dutch approved SPC of Augmentin, filmcoated tablets 500/125 mg and 875/125 mg. This text results from the article 30 procedure, which is published on the website of the EU Commission in October 2009.

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. Testing was performed with in total 20 participants. This cohort of 20 participants was recruited in the Geleen area, NL in the period October 2007. The way of recruitment and individual demographic and sociologic details were provided in the final report.

A total of fifteen questions have been evaluated with regard to the use of finding, ease of understanding and subjective impression of the PIL by the participants. The responses were recorded satisfactory. The user test showed that the leaflet enabled more than of the 90% of participants to find the information and more than 90% of those understood the information good or in detail. The overall impression of the methodology and the overall impression of the leaflet structure are positive.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amoxicilline/Clavulaanzuur Pfizer 500/125 and 875 mg/125 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Augmentin 500/125 mg and 875/125 mg filmcoated tablets. Augmentin 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, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. Amoxicilline/Clavulaanzuur Pfizer 500/125 and 875 mg/125 mg film-coated tablets are authorised in the Netherlands on 28 September 2010.

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 Amoxicilline/Clavulaanzuur Pfizer 500/125 and 875 mg/125 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 24 May 2011.

The PSUR submission cycle will follow the Harmonized Birth Date Amoxicillin/Clavulanic Acid. The EU harmonised birth date for Amoxicillin and clavulanate is 7 March 1972. The next Data Lock Point will be 31 March 2012, the company commits to submit PSUR in May 2012 to harmonise with the birthdate of Amoxicillin and clavulanate.

The date for the first renewal will be November 2012.

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

Quality - medicinal product

- The MAH has committed to validate a third batch (first commercial batch) at pilot-scale and the first three commercial batches for the three strengths, which will render additional batch results.

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 _{1/2}	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
<ul style="list-style-type: none"> - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations. - Change of the site undertaking pharmacovigilance activities. - Other change(s) to the DDPS that do not impact on the operation of the pharmacovigilance system. 	NL/H/2241/001-002/IA/111/G	IA/G	1-9-2011	3-10-2011	Approval	N