CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amoxicilline/Clavulaanzuur Aurobindo 500/125 mg and 875/125 mg, film-coated tablets Aurobindo Pharma Limited, United Kingdom

amoxicillin 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/1707/001-002/MR
Registration number in the Netherlands: RVG 33635-33636

15 June 2010

Pharmacotherapeutic group:	combinations of penicillins, incl. beta-lactamase inhibitors
ATC code:	J01CR02
Route of administration:	oral
Therapeutic indication:	acute bacterial sinusitis; acute otitis media; acute exacerbation of chronic bronchitits; 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:	22 February 2008
Concerned Member States:	Mutual recognition procedure with AT, BE, BG, CZ, DE, EE, EL, ES, FI, HU, IE, LT, LU, LV, PL, PT, RO, SE, SI, SK; DK and UK (only 500/125 mg); IT (only 875/125 mg strength)
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 Aurobindo 500/125 mg and 875/125 mg, film-coated tablets from Aurobindo Pharma Limited. The date of authorisation was on 22 February 2008 in the Netherlands.

The product is indicated for treatment of:
- acute bacterial sinusitis (adequately diagnosed)
- acute otitis media
- acute exacerbation 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.

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

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 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 film-coated tablets (NL License RVG 09840 and 18553) which have been registered in the Netherlands by GlaxoSmithKline B.V. since 2 December 1983 and 22 August 1996, respectively. 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 bioequivalence studies in which the pharmacokinetic profile of the 500/125 mg and 875/125 mg product is compared with the pharmacokinetic profile of the reference products Augmentin 500/125 mg tablets and Augmentan 875/125 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. These generic products can be used instead of their reference product.

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

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

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
The active substances are amoxicillin trihydrate and potassium clavulanate, established active substances described in the European Pharmacopoeia (Ph.Eur.*). Amoxillin trihydrate is a white or almost white, crystalline powder, which is slightly soluble in water, very slightly soluble in alcohol and practically insoluble in fatty oils. Potassium clavulanate is a white or almost white, hygroscopic powder, which is insoluble in water and acetone.

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 suitablity 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
For amoxicillin trihydrate specifications plus additional requirements as laid down in the CEP are applicable. The methods have been fully validated, and comparing batch results are available for 3 batches.
For potassium clavulanate specifications plus additional requirements from the involved CEPs are applicable. Batch analysis results for 3 batches are provided with results meeting the set Ph. Eur. and CEP requirements.

Stability of drug substance
The CEP for amoxicillin trihydrate states a re-test period of 2 years if stored under the proposed conditions. For potassium clavulanate from one CEP holder, a re-test period of 48 months is applicable. For the other CEP holder stability data were presented. Three batches of potassium clavulanate diluted have been stored at 2-8°C for 48 months, at 25°C/65% RH for 36 months, and at 40°C/75% RH for 6 months. All stability results met the drug substance specification. Based on these data the claimed re-test period of 4 years could be granted, when stored in the proposed packaging without specific storage condition.

* *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
Amoxicilline/Clavulaanzuur Aurobindo 500/125 mg contains as active substance 573.4 mg amoxicillin trihydrate equivalent to 500 mg amoxicillin and 277.8 mg potassium clavulanate equivalent to 125 mg clavulanic acid. The product is a white, oval, film coated tablets inscribed with ‘A’ on one side and ‘64’ on the other side.

Amoxicilline/Clavulaanzuur Aurobindo 875/125 contains as active substance 1003.4 mg amoxicillin trihydrate equivalent to 875 mg amoxicillin and 277.8 mg potassium clavulanate equivalent to 125 mg clavulanic acid. The product is a 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.

The different strengths are not dose-weight proportional.

The film-coated tablets are packed in Alu/Alu blister packs and Al/ Al strips in a cardboard box.

The excipients are:
Tablet core - microcrystalline cellulose (E460), colloidal silicum dioxide, magnesium stearate (E470b), sodium starch glycolate (type A).
Film-coating - hypromellose (E464), macrogol 400, titanium dioxide (E171).

Pharmaceutical development
The development was mainly based on the qualitative composition of the originator product Augmentan tablets for both strengths. In this development the requirements of the monograph Co-Amoxi-clav Tablets BP 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. The used excipients are all well known, pharmacopoeial substances, usual for the type of product, film-coated tablets.
The final 875/125 mg formulation was compared to Augmentan tablets 875/125 mg tablets in different dissolution media. In all media the dissolution profiles were comparable. Also the 500/125 mg proposed tablets have been compared with the corresponding UK originator products (Augmentin UK). Comparing dissolution studies were performed for two batches of both strengths of the proposed product, including the biobatch, using the DE and UK originator batches. The DE 875/125 mg reference product used in the bioequivalence study is acceptable in view of the composition of the NL originator product.
For amoxicillin trihydrate, an initial 3 % manufacturing overage is applied, due to losses during the manufacturing process. This has been adequately justified. The pharmaceutical development has been suficiently described.

Manufacturing process
The manufacturing process has been adequately described in sufficient detail, and adequate in-process controls have been listed. A sufficient number of batches per strength have been validated, including the 875+125 mg biobatch. Further validation will be performed post authorisation.

Control of excipients
All excipients except Opadry white coating mixture and purified water meet the full requirements of the corresponding Ph. Eur. monograph. The specifications are acceptable.

Quality control of drug product
Adequate specifications are proposed for the drug product. The specification includes tests for identification, average weight, uniformity of dosage units, dissolution, assay, related substances, water, water activity, microbial contamination, identification of colourants, thickness and residual solvents. Batch results have been provided for each strength, demonstrating compliance with the specification.

Stability of drug product
The stability results show that the tablets are sufficiently stable. For both components slight to moderate assay decreases are observed, but these are within the set requirements. Impurities increase during 24 months at 30°C/70% RH; these however remain within an acceptable maximum. Based on the stability data provided, the claimed shelf life of 2 years for both strengths without specific storage condition could be granted.

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

These products are a generic formulation of Augmentin film-coated tablets, which are 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 and 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 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 Amoxicilline/Clavulaanzuur Aurobindo 500/125 mg and 875/125 mg (Aurobindo Pharma Limited) is compared with the pharmacokinetic profile of the reference products Augmentin 500/125 mg tablets (GlaxoSmithKline, UK) and Augmentan 875/125 mg tablets (GSK, Germany), respectively.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

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

Bioequivalence study I: 500/125 mg
Design
An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 50 (48 + 2 alternates) healthy male subjects, aged 18-39 years. Each subject received a single dose (500/125 mg) of one of the 2 amoxicillin/ potassium clavulanate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 3 days.

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.

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

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

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

Treatment N=48	AUC_{0-t} µg.h/ml	$AUC_{0-\infty}$ µg.h/ml	C_{max} µg/ml	t_{max} h	$t_{1/2}$ h
Test	24.80 ± 5.36	25.37 ± 5.43	8.21 ± 2.29	2.0 (0.75 - 4.0)	1.16 ± 0.19
Reference	26.44 ± 6.04	26.92 ± 6.06	8.78 ± 2.68	2.0 (1.0 - 5.0)	1.15 ± 0.18
***Ratio (90% CI)**	0.95 (0.92-0.97)	0.94 (0.92-0.97)	0.94 (0.90-0.99)	-	-
CV (%)	8.1	7.9	14.9	-	-
$AUC_{0-\infty}$ 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 clavulanic acid under fasted conditions.

Treatment N=48	AUC_{0-t} µg.h/ml	$AUC_{0-\infty}$ µg.h/ml	C_{max} µg/ml	t_{max} h	$t_{1/2}$ h
Test	6.4 ± 2.52	6.62 ± 2.52	2.63 ± 0.98	1.25 (0.75 - 3.0)	1.10 ± 0.15
Reference	6.72 ± 2.41	6.96 ± 2.41	2.71 ± 0.96	1.5 (1.0 - 3.0)	1.13 ± 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	-	-
$AUC_{0-\infty}$ 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 amoxicillin and clavulanic acid under fasted conditions, it can be concluded that Amoxicilline/Clavulaanzuur Aurobindo 500/125 mg and Augmentin 500/125 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: 875/125 mg

Design

An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 50 (48 + 2 alternates) healthy Indian males, aged 19-40 years. Each subject received a single dose (875/125 mg) of one of the 2 amoxicillin/potassium clavulanate formulations. The tablet was orally administered with 240 ml water 30 minutes after a high fat

meal of 955 Kcal (approximately 60% of total calories consisted of fat). There were 2 dosing periods, separated by a washout period of 8 days.

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.

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

Results
One subject was dismissed for non-compliance (positive benzodiazepine test). Three subjects did not show up for Period II. The remaining 46 subjects completed the study.
Amoxicillin samples of 5 subjects and clavulanic acid samples of 3 subjects had already completed 3 freeze-thaw cycles when they came up for analysis. Stability of analytes beyond 3 freeze-thaw samples could not be established during analytical method validation. Therefore, for amoxicillin data of 41 of the 46 subjects who finished the study completely, were included in the statistical analyses. For clavulanic acid, data of 43 of the 46 subjects who finished the study completely, were included in the statistical analyses.

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

Treatment N=41	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml n=30	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	50.7 ± 8.9	51.4 ± 9.0	15.7 ± 3.5	2.33 (1-5)	1.5 ± 0.3
Reference	48.8 ± 8.6	49.4 ± 8.5	15.3 ± 3.4	2.33 (1.33-5)	1.5 ± 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	-	-

$AUC_{0-\infty}$ 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 clavulanic acid under fed conditions.

Treatment N=43	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml n=30	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4.0 ± 2.3	4.6 ± 2.5	1.9 ± 1.1	2.33 (1.33-5)	1.0 ± 0.2
Reference	3.7 ± 1.6	4.3 ± 1.7	1.7 ± 0.8	2 (1.33-3)	1.0 ± 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	-	-

$AUC_{0-\infty}$ 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 amoxicillin and clavulanic acid under fed conditions, it can be concluded that Amoxicilline/Clavulaanzuur Aurobindo 875/125 mg and Augmentan 875/125 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.

Food effect
The SPC states that the tablet should be taken with food to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid, which is in compliance with the innovator SPC. The bioequivalence study under fed conditions is therefore acceptable. There is, however, no pharmacokinetic reason for intake with food. Therefore the study under fasted conditions is also considered acceptable.

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
The combination of amoxicillin and clavulanate was first approved in 1972, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amoxicillin and 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 MAH will harmonise the SPC in accordance with SPC for Augmentin, within three months after publication of the product information resulting from the article 30 procedure, which was finalised in June 2009.

Readability test
Since the product information will be harmonised with the established texts for Augmentin, no readibilty test on the PIL was considered necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amoxicilline/Clavulaanzuur Aurobindo 500/125 mg and 875/125 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Augmentin 500/125 and 875/125 mg. 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 and are in agreement with the established texts for Augmentin.

The Board followed the advice of the assessors. Amoxicilline/Clavulaanzuur Aurobindo 500/125 mg and 875/125 mg were authorised in the Netherlands on 22 February 2008.

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 Aurobindo 500/125 mg and 875/125 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 22 September 2009.

A European harmonised birth date has been allocated (7 March 1972) and subsequently the first data lock point for amoxicillin + clavulanate is 31 March 2012. The first PSUR will cover the period from September 2009 to March 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 22 September 2014.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to perform further process validation as per protocol.

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
Submission of a new or updated Ph. Eur. certificate of suitability: For an active substance, for a starting material/reagent/ intermediate used in the manufacturing process of the active substance.	NL/H/1707/ 001-002/IA/ 001	IA	15-4-2010	15-5-2010	Approval	N
Changes in the specifications of potassium clavulanate, diluted in order to comply with the updated Ph. Eur. Monograph.	NL/H/1707/ 001-002/IA/ 002	IA	15-4-2010	15-5-2010	Approval	N