CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Cefuroximaxetil 125, coated tablets 125 mg
Cefuroximaxetil 250, coated tablets 250 mg
Cefuroximaxetil 500, coated tablets 500 mg
Sandoz B.V., the Netherlands

cefuroxime axetil

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/556/01-03/E01
Registration number in the Netherlands: RVG 26702-4

3 February 2010

Pharmacotherapeutic group:	cephalosporins and related substances
ATC code:	J01DA06
Route of administration:	oral
Therapeutic indication:	treatment of mild to moderately severe infections caused by micro-organisms susceptible to cefuroxime
Prescription status:	prescription only
Date of first authorisation in NL:	1 October 2004
Concerned Member States:	Repeat-use procedure with PT (only 250 and 500 mg) EE (250 mg and 500 mg withdrawn on 26 June 2008), EL (withdrawn on 28 April 2009), and ES
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) and 10(3) only in EE for 125 mg strength

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 Cefuroximaxetil 125/250/500, coated tablets 125/250/500 mg, from Sandoz B.V. The date of authorisation was on 1 October 2004 in the Netherlands.

The product is indicated for the treatment of mild to moderately severe infections caused by micro-organisms susceptible to cefuroxime, such as:
- upper respiratory tract infections: acute otitis media, sinusitis, tonsillitis and pharyngitis
- acute bronchitis, acute exacerbations of chronic bronchitis
- lower uncomplicated urinary tract infections: cystitis
- skin and soft tissue infections: furunculosis, pyoderma and impetigo
- treatment of early stage Lyme disease (stadium I) and subsequent prevention of late complications in adults and children above 12 years of age.

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

Cefuroxime axetil owes its *in vivo* bactericidal activity to the parent compound cefuroxime. All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug to cell receptors, called Penicillin-Binding Proteins. After a β-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. Bacterial lysis is the end result.

Repeat-use
On 26 January 2005, the mutual recoginition procedure NL/H/556/01-03/MR was ended positively for the present products for the following CMSs: AT, BE, CZ, HU, IE, LT, LU, LV, PL, SK and UK. The procedure was withdrawn from EE, ES, PT, IE (125 mg and 250 mg), LT (125 mg), LV (125 mg), and LU (250 mg). As stated in the "CMD(h) best practice guide for the public assessment report in the decentralised and mutual recognition procedures", member states will actively publish a PAR for all DCPs and MRPs ended after 30 October 2005. As NL/H/556/01-03/MR ended on 26 January 2005, no PAR is available for the initial mutual recognition procedure.
However, a repeat Use Procedure was started for the CMSs PT (only 250 and 500 mg) EE, EL, and ES on 28 March 2006. In this PAR the repeat-use procedure has been described. The procedure was withdrawn from EE and EL (250 and 500 mg).

This repeat-use procedure concerns a generic application claiming essential similarity with the innovator product Zinnat 125, 250, and 500 mg film-coated tablets (NL license RVG 13225-7), which has been registered in the Netherlands by GlaxoSmithKline B.V since 1989. In addition, reference is made to Zinnat authorisations in the individual member states.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In EE, the marketing authorization for the 125 mg tablets is granted based on article 10(3) 'hybrid application', as Zinnat 125 mg is not registered in Estonia. Reference is made to the innovator product Zinnat 500 mg in EE, which is acceptable.

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 product Zinnat 500 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.

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 cefuroxime axetil, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Cefuroxime axetil is a pro-drug of the active compound Cefuroxime, which is a second generation cephalosporin. Cefuroxime axetil is slightly soluble in water and freely soluble in acetone. The molecular structure of Cefuroxime axetil is well characterized. The oxime moiety of the structure (C=N) can exist in the Z- and E-isomeric form.
Cefuroxime axetil is a mixture of two diastereoisomers. A specification for diastereoisomer ration and for specific optical rotation is included in the monograph.
Cefuroxime axetil exhibits polymorphism. Since the active substance is dissolved in acetone and purified water during the manufacturing of the finished product, polymorphic forms and particle size distribution of the active substance will have no influence on the quality of the finished product.

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 synthesis comprises five reaction steps, followed by a purification step utilizing decolourisation and subsequent filtration and recrystallisation. No class 1 organic solvents and heavy metal catalysts are used. The active substance has been adequately characterized. Acceptable specifications have been adopted for the starting material, solvents and reagents.

Specification
The drug substance specification is in line with the Ph.Eur. with additional requirements for some specified in-house impurities (E,F,G) and residual solvents. The specification is acceptable in view of the route of synthesis and the various European guidelines. The limits for the in-house impurities are qualified. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches, complying with the specification limits.

Stability
Stability data on the active substance have been provided for three full scaled batches and three pilot scaled batches stored at 25°C/60% RH (full scaled batches: 24 months, pilot batches: 36 months) and 40°C/75% RH (six months). The batches were adequately stored. On the basis of the stability studies it was decided that the drug substance will be tested prior to use in the manufacture of the product to ensure compliance with its specification.

The results of these stability studies were submitted by means of a type II variation (NL/H/556/001-003/II/013). Stability data on the active substance were provided for three full scaled batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (six months). The batches were adequately stored. An adequate re-test period has been defined based on conducted stability studies.

** Ph.Eur. is an official handbooks (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
The product is a coated tablet, containing Cefuroxime axetil equivalent with 125 mg, 250 mg and 500 mg Cefuroxime respectively.

The tablets appear as follows:
Cefuroximaxetil 125: white to slightly yellowish, biconvex, oblong tablets
Cefuroximaxetil 250: white to slightly yellowish, biconvex, oblong tablets, scored on both sides. The tablet can be divided into equal halves.
Cefuroximaxetil 500: white to slightly yellowish, biconvex, oblong tablets

The tablets are packed in Al/Al strip packaging, or Al/Al blister packaging.

The excipients are:
Tablet core: sodium lauryl sulphate, copovidone, croscarmellose sodium (E468), magnesium stearate (E470B), colloidal anhydrous silica (E551), granulated mannitol (E421), microcrystalline cellulose (E460), crospovidone (E1202), and talc (E553B).

Tablet coating: mannitol (E421), soluble starch (potato), talc (E553B), titanium dioxide (E171), aspartame (E951).

The contents of the 3 tablet formulations, 125, 250 and 500 mg, are dose proportional.

Pharmaceutical development
The excipients and packaging are usual for this type of dosage form. The development of the product has been described, the choice of excipients is justified and their functions explained. The tablets are coated to mask the bitter taste of the tablets.
The MAH did not use the 125 and 250 mg tablets in the bioequivalence study. From a chemical-pharmaceutical point of view this is no objection since all three strengths are dose proportional with regard to the core of the tablet. Therefore, no influence is expected on the bio-availability for the difference in strength which is supported by the *in vitro* dissolution profiles. The reference batch was Zinnat 500 mg, Glaxo Wellcome GmbH & Co (DE). The qualitative and quantitative formula and the manufacturer of the reference product are identical to the qualitative and the quantitative formula and the manufacturer of the innovator product marketed in the Netherlands. All reference batches from the different CMS countries show comparable dissolution profiles, indicating that the use of the German reference product is representative.
The pharmaceutical development of the product has been adequately performed.

Excipients
The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs except for soluble starch (potato), which complies with in-house specifications. The specifications are acceptable.

Manufacturing process
The manufacturing process is a standard process, using conventional manufacturing techniques, comprising wet granulation steps, blending, tabletting of the blend mass and coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for 2 pilot scaled batches per tablet strength. The MAH

committed to perform a process validation on the first three full-scale production batches per dosage strength.

Product specification
The product specification includes tests for appearance (shape, sizes, colour), identity, hardness, assay, degradation products, water content, uniformity of mass, dissolution and microbial purity.
The release and shelf-life requirements/limits are identical except for water content, assay and degradation products. They are acceptable in view of the batch analysis results and stability studies. Limits for degradation products are qualified. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on 2 pilot scale batches per tablet strength, demonstrating compliance with the release specification. The MAH committed to submit a Certificate of analysis of the first three production scale batches per dosage strength.

Breakability:
The 250 mg tablets contain a score line. Therefore, the MAH has performed tests on breakability of two batches of the 250 mg tablets. The results comply with Ph. Eur at the extremes of the specification for hardness (90N and 150N for the 250 mg tablets).

Stability tests on the finished product
Stability data on the product have been provided of numerous pilot scale batches per tablet strength of different sizes, and also two production scaled batches of the 125 mg strength. Most of the batches were stored during 36 months at 25°C/60% RH, 12 months at 30°/65% RH and six months at 40°C/75% RH. The full scale batches were stored during 12 months at 25°C/60% RH and 30°/65% RH and six months at 40°C/75% RH. The storage conditions in the stability studies are according to the ICH stability guideline. The batches were stored in the approved Aluminium/Aluminium strips and - blisters.
The proposed shelf-life of '*36 months in Al/Al blisters, no special storage temperature, store in the original package' and '36 months in Al/Al strips, no special storage temperature, store in the original package*' are justified. The MAH has committed to submit the stability data of ongoing stability studies up to the end of the shelf-life, together with the data on the three first production scale batches per dosage strength.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Zinnat, 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 cefuroxime axetil 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

Cefuroxime axetil is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Cefuroximaxetil 500 mg tablets (Sandoz B.V.) is compared with the pharmacokinetic profile of the German reference product Zinnat 500 mg tablets (Glaxo Wellcome, Germany).

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

Bioequivalence study under fed conditions

A single-dose, open, randomised, two-way, crossover bioequivalence study was carried out under fed conditions in 20 (10 male, 10 female) healthy volunteers, aged 19-41 years. Each subject received a single dose (500 mg) of one of the 2 cefuroxime axetil formulations. The tablet was orally administered with 240 ml water, 0.5 hour after a standard breakfast (two rolls (40 g each), 20 g butter, 40 g jam and 240 ml of rose hip tea). There were 2 dosing periods, separated by a washout period of 6 days. Blood samples were collected predose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, and 10 hours after administration of the products. All 20 subjects were eligible for pharmacokinetic analysis.

The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The long term stability data are covering the storage period of the plasma samples.

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

Treatment N=20	**AUC_{0-t}** mg.h/ml	**$AUC_{0-\infty}$** mg.h/ml	**C_{max}** mg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	22.5 ± 4.2	22.9 ± 4.3	6.9 ± 1.2	1.67 (1.0 – 3.5)	1.1 ± 0.1
Reference	22.0 ± 4.2	22.4 ± 4.3	6.4 ± 0.9	2.0 (1.33 – 3.5)	1.1 ± 0.1
***Ratio (90% CI)**	1.02 (1.00 - 1.04)	1.02 (1.00 - 1.04)	1.07 (1.01 - 1.13)	---	---
CV (%)	3.5	3.6	10.2	---	---

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

**ln-transformed values*

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 cefuroxime axetil under fed conditions, it can be concluded that Cefuroxime axetil 500 mg tablets and the Zinnat 500 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.

The 125 mg and 250 mg tablets are dose-proportional with the 500 mg tablet. Therefore, no bioequivalence study has to be carried out with these formulations, as the results obtained for the 500 mg tablet can be extrapolated to the 125 mg and 250 mg tablets.

GCP and GLP

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).

Referral to CMD(h) and CHMP

During the procedure a potential serious risk to public health was raised. One CMS could not accept the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' and two CMSs could not accept the indication 'Treatment of early stage Lyme disease (stadium 1) and subsequent prevention of late

complications in adults and children above 12 years of age'. In addition one CMS requested inclusion of Community Acquired Pneumonia (CAP). The issue was therefore referred to the CMD(h).
The CMD(h) was able to reach agreement on the approval of the indication 'Treatment of early stage Lyme disease (stadium 1) and subsequent prevention of late complications in adults and children above 12 years of age'. In addition, the CMD(h) was able to reach agreement not to include CAP to the indications. On the indication "'Uncomplicated gonorrhoea: urethritis and cervicitis" no agreement was reached. Spain therefore referred the procedure on 25 September 2006 to the CHMP under Article 29(4) of Directive 2001/83/EC as amended for arbitration.

The arbitration procedure started on 18 October 2006 with the adoption of a list of questions.
During their April 2007 meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, an opinion was adopted that the objections raised by Spain could be agreed and that the SPC, labelling and package leaflet of the RMS should be amended. CHMP considered that insufficient evidence was provided to support the optimal efficacy of cefuroxime axetil in treating uncomplicated gonorrhoea, restricted to urethritis and cervicitis. The efficacy of cefuroxime axetil on other anatomical locations, (which often remain asymptomatic), is highly questionable and consequently treatment with cefuroxime axetil might not curtail further transmission of the infection. Therefore, the inclusion of uncomplicated gonococcal disease is a matter of major concern from a public health perspective, both at individual and community level. Therefore, it was decided that the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' will be removed from the SPC of the innovator product by an article 31 (Directive 2001/83/EC as amended) procedure.

After the CHMP Referral it was decided to change the Referral procedure for the innovator product into an Article 30 (Directive 2001/83/EC as amended) procedure, enabling a thorough review of the product information. Existing Marketing Authorisations should be varied and pending Marketing Authorisation Applications should be granted to include these amendments.

Risk management plan
Cefuroxime axetil was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of cefuroxime axetil 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 SmPC assessment was based on the Innovator product Zinnat in the Netherlands. The SPC is identical to the day 90 SPC of the first use MRP NL/H/556/01-03, except for the removal of the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' and the inclusion of a warning in section 4.4 regarding the long term use of cefuroxime axetil.

Readability test
Before the start of this repeat-use procedure the MAH has put the approved Patient Information Leaflet (PIL) into the new template. A readability test for this PIL was not performed. Due to the high similarity between this PIL and the PIL for another Cefalosporine-containing product (Cefpodoxim), the MAH has decided to "bridge" the PIL readability test of these products.

To comply with the Consultation with Target Patients Groups the MAH previously submitted a bridging statement. This was submitted as part of the dossier during the procedure NL/H/0556/001-003/II/010, NL/H/0557/001-003/MR and NL/H/0558/001-003/MR.
The patient leaflet was bridged to Cefpodoxim proxetil 40 mg/5 ml Powder for Oral Solution. The user testing for the patient leaflet of Cefpodoxim proxetil 40 mg/5 ml Powder for Oral solution was approved in

procedure UK/H/0851-0854/001-003/MR (March 2006). The PIL for Cefpodoxim was tested. In view of the positive user test for Cefpodoxim, changes have been made to the Cefuroxime axetil PIL.

The RMS concur with the conclusion that the content and format of the untested Cefuroxime axetil PIL is sufficiently similar to the content and format of the user tested Cefpodoxim. Results of the Cefpodoxim user test can be applied to the present Cefuroxime axetil PIL. The PIL has been approved in the variation NL/H/0556/001-003/II/010.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Cefuroximaxetil 125/250/500, coated tablets 125/250/500 mg have a proven chemical-pharmaceutical quality and are a generic form of Zinnat tablets. Zinnat 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 Board followed the advice of the assessors during the national registration in the Netherlands. Cefuroximaxetil 125/250/500 mg tablets were authorised in the Netherlands on 1 October 2004.

During the repeat-use procedure a potential serious risk to public health was raised. One CMS could not accept the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' and two CMSs could not accept the indication 'Treatment of early stage Lyme disease (stadium 1) and subsequent prevention of late complications in adults and children above 12 years of age'. In addition one CMS requested inclusion of Community Acquired Pneumonia (CAP). The issue was therefore referred to the CMD(h).
The CMD(h) was able to reach agreement on the approval of the indication 'Treatment of early stage Lyme disease (stadium 1) and subsequent prevention of late complications in adults and children above 12 years of age'. On the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' no agreement was reached. In addition, the CMD(h) was able to reach agreement not to include CAP to the indications.
Subsequently, the procedure was referred to the CHMP under Article 29(4) of Directive 2001/83/EC. During their April 2007 meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, was of the opinion that the objections raised by Spain could be agreed and that the SPC, labelling and package leaflet of the RMS should be amended. The indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' was removed from the SPC, and a warning was included regarding the long term use of cefuroxime axetil. Existing Marketing Authorisations should be varied and pending Marketing Authorisation Applications should be granted to include these amendments. An opinion was adopted on 26 April 2007.

The final opinion was converted into a Decision by the European Commission on 22 August 2007. On the basis of the data submitted, the concerned member states have granted a marketing authorisation.

In the Board meeting of 3 May 2007, a discussion was held regarding the start of an Article 31 procedure for the innovator for the indication 'uncomplicated gonorrhoea: urethritis and cervicitis'.

The SPC is consistent with that of the reference product, except for the removal of the indication 'Uncomplicated gonorrhoea: urethritis and cervicitis' and the inclusion of a warning in section 4.4 regarding the long term use of cefuroximaxetil. The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from May 2003 to April 2009.

The date for the first renewal will be: 26 January 2010.

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

<u>Quality - medicinal product</u>
- The MAH committed to perform a process validation on the first three full-scale production batches per dosage strength.
- The MAH committed to submit a Certificate of analysis of the first three production scale batches per dosage strength.
- The MAH has committed to submit the stability data of ongoing stability studies up to the end of the shelf-life, together with the data on the three first production scale batches per dosage strength.

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
MA	Marketing authorization
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
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0556/ 002-003/IA/ 001	IA	31-3-2005	31-3-2005	Non approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/0556/ 001-003/IA/ 002	IA	31-3-2005	31-3-2005	Non 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 outside the range of the currently approved pack sizes.	NL/H/0556/ 001-003/IA/ 003	IA	31-3-2005	31-3-0005	Non approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0556/ 002-003/IA/ 004	IA	---	3-5-2005	Non approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/0556/ 001-003/IA/ 005	IA	27-4-2005	25-5-2005	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 outside the range of the currently approved pack sizes.	NL/H/0556/ 001-003/IA/ 006	IA	27-4-2005	25-5-2005	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0556/ 002-003/IA/ 007	IA	14-6-2005	28-6-2005	Approval	N
Change in the name and/or address of the marketing authorization holder.	NL/H/0556/ 001-003/IA/ 008	IA	23-6-2005	7-7-2005	Approval	N
Change in ATC code, medicinal products for human use.	NL/H/0556/ 001-003/IA/ 009	IA	22-9-2005	6-10-2005	Approval	N
New Legislation: Harmonisation of PIL and Labelling in both old CMS and new CMS of Repeat Use Procedure.	NL/H/0556/ 001-003/II/ 010	II	28-3-2006	26-6-2006	Approval	N
Withdrawal of the marketing authorization in Greece on 26 June 2008	NL/H/0556/ 002-003/E/ 001	Withdrawal	---	26-6-2008	---	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules. Consequential change IA no.7a.	NL/H/0556/ 001-003/IA/ 011	IA	19-6-2008	3-7-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the	NL/H/0556/ 001-003/IB/ 012	IB	1-7-2008	31-7-2008	Approval	N

finished product. All other manufacturing operations except batch release.						
Withdrawal of the marketing authorization in Estonia on 28 April 2009	ML/H/0556/ 001-003/E/ 001	Withdrawal	---	28-4-2009	---	N
Update DMF.	NL/H/0556/ 001-003/II /013	II	30-12-2008	12-11-2009	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. Addition of pack size of 16.	NL/H/0556/ 002/IA/014	IA	28-6-2009	13-7-2009	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. Addition of pack size 16.	NL/H/0556/ 003/IA/015	IA	30-6-2009	14-7-2009	Approval	N
Deletion of test parameter "absorbance" from the specification of the non-compendial excipient starch, soluble.	NL/H/0556/ 001-003/II /016	II	16-7-2009	14-9-2009	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 outside the range of the currently approved pack sizes. Additional of pack size of 500 tablets in blister as hospital package.	NL/H/0556/ 001/IB/017	IB	4-11-2009	4-12-2009	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 outside the range of the currently approved pack sizes. Additional of pack size of 500 tablets in blister as hospital package.	NL/H/0556/ 002/IB/018	IB	4-11-2009	4-12-2009	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 outside the range of the currently approved pack sizes. Additional of pack size of 500 tablets in blister as hospital package.	NL/H/0556/ 003/IB/019	IB	4-11-2009	4-12-2009	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/0556/ 001-003/ IA/020	IA	28-9-2005	28-9-2005	Non-approval	N