CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Pantoprazol Sandoz 20 mg, gastro-resistant tablets
Pantoprazol Sandoz 40 mg, gastro-resistant tablets
Sandoz B.V., the Netherlands

pantoprazole sodium sesquihydrate

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/0751/001-002/DC
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Pharmacotherapeutic group:	drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors
ATC code:	A02BC02
Route of administration:	oral
Therapeutic indication:	duodenal and benign gastric ulcers; Zollinger-Ellison syndrome; gastro-oesophageal reflux disease
Prescription status:	prescription only
Date of authorisation in NL:	23 November 2007
Concerned Member State:	Decentralised procedure with DE and ES
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 concerned member states have granted a marketing authorisation for Pantoprazol Sandoz 20 mg and 40 mg gastro-resistant tablets from Sandoz B.V. The date of authorisation in the Netherlands was on 23 November 2007.

The 20 and 40 mg strengths have different indications.

The 20 mg strength is indicated for:
- The treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).
- Long-term management and prevention of relapse in reflux oesophagitis.
- Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment.

The 40 mg strength is indicated for:
- In combination with two suitable antibiotics for the eradication of Helicobacter pylori in patients with peptic ulcers with the goal to reduce the possibility of a recurrence of duodenal ulcer and gastric ulcer caused by micro-organisms.
- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis
- Zollinger-Ellison syndrome and other disorders involving pathological hypersecretion.

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

Pantoprazole is a proton pump inhibitor with significant gastric anti-secretory effects. Today, pantoprazole is used in the treatment of gastroesophageal reflux disease (GERD), in the treatment of pathological hypersecretory states such as the Zollinger-Ellison syndrome, in the treatment of gastric and duodenal ulcers, and for the eradication of Helicobacter pylori in combination with two antibacterials in a triple therapy regimen. The drug has also been used successfully in the prophylaxis for NSAID-associated ulceration. The drug can be used either as monotherapy or in combination, for example, with antacids or, as in the case of triple therapy regimens for the eradication of Helicobacter infection, with antibacterials.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Somac® 40 mg gastro-resistant tablets. The innovator product has been registered by Nycomed GmbH since 7 November 1994 in Finland. In addition, reference is made to Somac® authorisations (other names for the innovator product are amongst others Pantoc®, Pantorc®, Pantoloc®, Pantozol®) 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 applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product, Pantaloc® 40 mg tablets, by Altena Pharma registered in Denmark. Pantaloc is the name for the innovator product in Denmark. 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 preclinical and clinical studies were conducted, which is acceptable for this abridged 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 authorisations.

Active substance and excipients
The active substance is pantoprazole sodium sesquihydrate. There is no Ph.Eur.* monograph on pantoprazole sodium sesquihydrate, but a draft Ph.Eur. monograph exists (XXXX: 2296, Pharmeuropa 18.2, April 2006). This draft has been used as guidance. (Note: The official monograph was published in the Ph.Eur. in April 2008.) The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 5 batches.
The MAH provided adequate information on the crystalline form of the drug substance by X-ray diffraction studies. As a post-approval commitment the MAH committed that the drug substance will meet the same crystalline form of pantoprazole sodium sesquihydrate.

There are three suppliers of the active substance. For all suppliers 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/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

All three ASMs have submitted stability data on the active substance. For each supplier stability data have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over at least 24 months. Based on the data submitted, adequate retest periods have been granted for each manufacturer.

The excipients are well-known pharmacopoeial substances and usual for a gastro-resistant tablet formulation. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs, except for iron oxide yellow (E172) and the intermediate coating layer, i.e. opadry yellow. For iron oxide yellow (E172) the USP* specifications were used, whereas for the coating layer 'opadry yellow' in-house specifications were provided.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA, respectively.*

Medicinal Product

Composition
Pantoprazol Sandoz 20 mg and Pantoprazol Sandoz 40 mg contain 20 mg pantoprazole (as pantoprazole sodium sesquihydrate) and 40 mg pantoprazole (as pantoprazole sodium sesquihydrate), respectively. The 20 and 40 mg coated tablets are yellow and oval. After the type IA variation NL/H/0751/001-002/IA/001 the tablets imprinted 20 respectively 40 in black.

The tablets are supplied in Al/OPA/Al/PVC blister packaging or HDPE tablet container with polypropylene screw cap including a desiccant insert.

The excipients are:
Tablet core calcium stearate, cellulose microcrystalline, crospovidone, hydroxypropylcellulose (type EXF), sodium carbonate anhydrous, silica colloidal anhydrous
Coating hypromellose, iron oxide yellow (E172), macrogol 400, methacrylic acid – ethyl acrylate copolymer (1:1), polysorbate 80, ponceau 4R aluminium lake (E124), quinoline yellow aluminium lake (E104), sodium lauryl sulphate, titanium dioxide (E171), triethyl citrate
Printing ink macrogol 600, shellac, povidone, iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172)

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Pantoprazole is acid labile and is therefore formulated as a delayed-release tablet with an enteric coat. This ensures that absorption, although rapid, occurs only after the tablet leaves the stomach. Pantoprazole is labile particularly < pH 5.5, and sensitive for moisture. The use of single-unit non-disintegrating dosage forms is acceptable because the same formulation principles are applied in the well-known originator product. The functionality of the enteric coating is pivotal, and in the full-scale validation study the manufacturing and functionality of the enteric coating has been satisfactorily validated using numerous representative samples for the enteric coating step and the final product. The proposed formulation and applied control tests c.q. specifications can be accepted.

The objective was to develop a product that would be bioequivalent with the innovator product Somac® 40 mg.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 full-scale batches of each strength in accordance with the relevant European guidelines, including the as critical step regarded enteric coating step.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for identification, uniformity of dosage units, disintegration, dissolution, gastro-resistance, related substances, microbiological quality, assay and identification of colorants. The MAH agreed that an additional visual identification element should be added to the coated tablets. Prior to marketing, the MAH committed to apply for a variation adding imprint ‘20’ respectively ‘40’ in order to differentiate between the product strengths. (See also ‘Steps taken after the finalisation of the initial procedure’, page 10). Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for 2 pilot-scale batches of each strength have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 2 batches of each strength in accordance with applicable European guidelines demonstrating the stability of the product for 24 months; in both alu-alu blister as well as HDPE container. On the basis of the data submitted, a shelf life can be granted of 3 years in alu-alu blister packaging or HDPE tablet container and polypropylene closure with desiccant insert, without a specific storage temperature. The MAH committed to put 2 full-scale batches, for each strength, on stability.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and 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 Somac, 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 identical products on the market. The approval of this product will not result in an increase in the total quantity of pantoprazole sodium sesquihydrate 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

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

The content of the SPC approved during the decentralised procedure is in accordance with the SPC of the innovator product.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Pantoprazol Sandoz 40 mg is compared with the pharmacokinetic profile of the reference product Pantaloc 40 mg (Pantaloc is the name for the innovator product in Denmark). Pantoprazole pharmacokinetics is linear, and pantoprazole does not accumulate upon multiple dose administration. Considering the pharmacokinetic profile, a single-dose study under fasted conditions and under fed conditions is considered adequate.

Single-dose study under fasting conditions
A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-55 years. Each subject received daily a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after a 10 hour fast. For each subject there were 2 dosing periods, separated by a washout period of at least 7 days. Two subjects withdrew from the study for personal reasons. Thirty-eight volunteers completed the study and were eligible for pharmacokinetic evaluation. The bioavailability of the test Pantoprazol Sandoz 40 mg tablet was compared to the reference product Pantaloc 40 mg tablet (Altena Pharma, Denmark).

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

Treatment N=38	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5561 ± 792	6331 ± 1257	2423 ± 126	2.67 (1.33-5.0)	1.53 ± 0.23
Reference	5619 ± 786	6498 ± 1319	2631 ± 146	2.33 (1.33-4.5)	1.59 ± 0.25
***Ratio (90% CI)**	0.99 (0.95-1.04)	0.99 (0.94-1.03)	0.93 (0.88-0.99)	--	--
CV (%)	11.8	11.3	14.3	--	--

$AUC_{0-\infty}$	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

Two subjects had a residual area above 20%.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. The statistical analysis of the pharmacokinetic data was adequate. No statistically significant period effect was noted. Based on the pharmacokinetic parameters of pantoprazole under fasting conditions, it can be concluded that test Pantoprazol Sandoz 40 mg tablet and the Danish reference Pantaloc 40 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Single-dose study under fed conditions

A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fed conditions in 74 healthy male subjects, aged 20-55 years. Each subject received daily a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after intake of a high-fat breakfast. For each subject there were 2 dosing periods, separated by a washout period of at least 7 days. There were six withdrawals, i.e. three subjects withdrew for personal reasons and three withdrew due to adverse events. Pharmacokinetic parameters were determined per protocol for the subjects, who completed the study. The bioavailability of the test Pantoprazol Sandoz 40 mg tablet was compared to the reference product Pantaloc 40 mg tablet (Altena Pharma, Denmark).

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

Treatment N=68	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5565 ± 4534	5970 ± 5916	2453 ± 751	7.0 (2.0-22)	1.6 ± 1.5
Reference	5977 ± 4853	6327 ± 6137	2768 ± 771	6.0 (3.0-22)	1.5 ± 1.5
***Ratio (90% CI)**	0.93 (0.91-0.95)	0.93 (0.91-0.96)	0.88 (0.83-0.92)	--	--
CV (%)	61.8	65.2	25.0	--	--

$AUC_{0-\infty}$	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 within the bioequivalence acceptance range of 0.80-1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of both pantoprazole under fed conditions, it can be concluded that test Pantoprazol Sandoz 40 mg tablet and the Danish reference Pantaloc 40 mg tablet are bioequivalent with respect to rate and extent of absorption after a high-fat breakfast, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 20 mg gastro-resistant tablets are dose proportional with the 40 mg gastro-resistant tablets. The pharmacokinetics of the active substance are linear in the range 20-40 mg. Comparable dissolution of the

20 and 40 mg tablets has been sufficiently demonstrated. The results of the bioequivalence study performed with the 40 mg strength therefore apply to the 20 mg strength.

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 concerned member states.

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

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

Pantoprazole was for the first time approved in 1994 in the European Union, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of pantoprazole can be considered to be well-established and no product-specific pharmacovigilance issues were identified pre- or post authorisation, 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 Risk Management Plan is not necessary for this product.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed. The test process involved two rounds with 12 participants each. The participants were an adequate reflection of a possible patient population with respect to age, gender and education.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Pantoprazol Sandoz 20 mg gastro-resistant tablets and Pantoprazol Sandoz 40 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Somac®. Somac 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 SPC is consistent with that of the innovator product.

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. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Pantoprazol Sandoz 20 mg and Pantoprazol Sandoz 40 mg with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between the concerned member states was reached during a written procedure.

A European harmonised birth date has been allocated (23-08-1994) and subsequently the first data lock point for pantoprazole is August 2009. The first PSUR is therefore expected in October 2009, after which a PSUR should be submitted every 3 years.

The first renewal date is on 15 May 2010.

The following post-approval commitments were made during the procedure:

Quality – active substance

- The MAH committed that the drug substance will meet the same crystalline form of pantoprazole sodium sesquihydrate.
- The MAH committed to test all batches of the drug substance on X-ray diffraction according to the specification on polymorphism.

Quality – medicinal product

- The MAH committed, prior to marketing of the product, to apply for a variation adding imprint ‘20’ respectively ‘40’ in order to differentiate between the product strengths. This commitment has been fulfilled (See table below, NL/H/0751/001-002/IA/001).
- The MAH committed to use all batch control sites only when transfer of analytical methods has been successfully performed.
- The MAH committed to submit certificates of analysis from all batch control sites, made after the analytical transfer.
- The MAH committed to put 2 full-scale batches of each strength on stability.

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
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RH	Relative Humidity
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 procedure	Approval/ non approval	Assessment report attached Y/N
Addition of imprint on tablets used for product marketing. Guideline pt. 39.	NL/H/0751/001-002/IA/001	IA	24-10-2007	9-11-2007	Approved	N
Change in the name of the medicinal product in Spain.	NL/H/0751/001-002/IB/002	IB	31-10-2007	3-12-2007	Approved	N
Update of a CEP for calcium stearate.	NL/H/0751/001-002/IA/003	IA	22-10-2008	5-11-2008	Approved	N
Change from batch size range to specific batch size.	NL/H/0751/001-002/IB/004	IB	29-10-2008	28-11-2008	Approved	N
Change to batch release arrangements and quality control testing of the finished product; addition of a manufacturer responsible for batch release; not including batch control/testing.	NL/H/0751/001-002/IA/005	IA	3-3-2009	17-3-2009	Approved	N
Replacement or addition of a manufacturing site for part of all of the manufacturing process of the finished product; primary packaging site.	NL/H/0751/001-002/IA/006	IA	5-3-2009	19-3-2009	Approved	N
Replacement or addition of a manufacturing site for part of all of the manufacturing process of the finished product; primary packaging site.	NL/H/0751/001-002/IA/007	IA	5-3-2009	19-3-2009	Approved	N
Change in the specification of the finished product – addition of a new test parameter.	NL/H/0751/001-002/IB/008	IB	4-6-2009	4-7-2009	Approved	N
Change in the name of the medicinal product in germany.	NL/H/0751/001-002/IB/009	IB	27-4-2009	27-5-2009	Approved	N
Additional bulk manufacturing site; scale-up at additional manufacturing site; addition of printing ink and thinners.	NL/H/0751/001-002/II/010	II	20-7-2009	21-9-2009	Approved	N
Change of legal status from UR to OTC.	NL/H/0751/001-002/II/011	II	2-9-2009	2-11-2009	Approved	N
Deletion of a packaging site.	NL/H/0751/001-002/IA/012	IA	1-9-2009	15-9-2009	Approved	N
Deletion of a packaging site.	NL/H/0751/001-002/IA/013	IA	1-9-2009	15-9-2009	Approved	N
Change to batch release arrangements and quality control testing of the finished product; addition of a manufacturer responsible for batch release; including batch control/testing.	NL/H/0751/001-002/IA/014	IA	18-9-2009	2-10-2009	Approved	N
After Ph. Eur. monograph Pantoprazole Sodium Sesquihydrate (04/2008:2296) has been published in April 2008, the quality standard recommended by the monograph has been adopted by drug product manufacturer and also by API supplier.	NL/H/0751/001-002/IB/015	IB	18-9-2009	19-10-2009	Approved	N
Change in batch size of active substance, Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/0751/001-002/IA/016	IA	21-10-2009	4-11-2009	Approved	N
Change in the name of the medicinal product in germany and Spain.	NL/H/0751/001-002/IB/017	IB	23-11-2009	23-12-2009	Approved	N
Minor change in the manufacturing process of the active substance.	NL/H/0751/001-002/IB/018	IB	19-12-2009	18-1-2010	Approved	N
Change in the specification of an active substance or a starting material/ intermediate/reagent used in the manufacturing process of the active substance; tightening of specification limits.	NL/H/0751/001-002/IA/019	IA	15-12-2009	29-12-2009	Approved	N
Change in batch size of active substance; up to 10-fold compared to the original batch size approved at the grant of the	NL/H/0751/001-002/IA/020	IA	16-12-2009	30-12-2009	Approved	N

marketing authorisation						
Change in the address of manufacturer of the active substance where no Europoean Pharmacopoeia certificate of suitability is available.	NL/H/0751/001-002/IA/021	IA	16-12-2009	30-12-2009	Approved	N