CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Olanzapine Synthon 2,5/5/7,5/10/15/20 mg tablets
Synthon B.V., the Netherlands

olanzapine (as benzoate)

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/965/001- 006/DC
Registration number in the Netherlands: RVG 34649-34654

8 July 2011

Pharmacotherapeutic group:	diazepines, oxazepines, thiazepines and oxepines
ATC code:	N05AH03
Route of administration:	oral
Therapeutic indication:	schizophrenia; moderate to severe manic episode
Prescription status:	prescription only
Date of authorisation in NL:	3 March 2009
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, LT, LU, LV, NO, PL, PT, SE, SI, SK, and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Olanzapine Synthon 2,5/5/7,5/10 mg tablets, from Synthon B.V. The date of authorisation was on 3 March 2009 in the Netherlands. The product is indicated for:

- treatment of schizophrenia.
- maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.
- treatment of moderate to severe manic episode.
- in patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder.

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

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems. Olanzapine is a member of the so-called atypical antipsychotics, as opposed to the classical antipsychotics, such as haloperidol, showing greater affinity to Serotonin $5HT_{2A}$-receptors than to Dopamine D_2-receptors. Atypical antipsychotics would elicit fewer extra pyramidal symptoms and would have an effect on the negative symptoms of the disease.
In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki; < 100 nM) for serotonin 5-$HT_{2A/2C}$, 5-HT_3, 5-HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors m_1-m_5; α-$_1$ adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in-vitro* affinity for serotonin 5-HT_2 than dopamine D_2 receptors and greater 5-HT_2 than D_2 activity *in vivo*, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.
The efficacy and safety of olanzapine has been demonstrated in randomised, placebo-controlled and comparative trials in positive and negative symptoms of schizophrenia, and also as monotherapy or in combination with mood stabilizers in the treatment of acute manic or mixed episodes associated with bipolar disorder. A summary of these studies may be found in the EPAR of Zyprexa to be found on website of the EMA (http://www.ema.europa.eu/humandocs/PDFs/EPAR/olanzapine_mylan/H-961-en6.pdf).

This decentralised procedure concerns a generic application claiming essential similarity with Zyprexa 2.5, 5, 7.5, 10, 15, and 20 mg coated tablets (EU License EU/1/96/022) which have been registered through a centralised procedure by Eli Lilly Nederland B.V. since 1996).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

Withdrawal of 15 mg and 20 mg
During the procedure, *in vivo* bioequivalence could not be demonstrated for the 15 mg and 20 mg tablets. Therefore, these strengths were withdrawn by the applicant. See *II.3 Clinical aspects*.

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 one bioequivalence study in which the pharmacokinetic profile of the product is compared with

the pharmacokinetic profile of the reference product Zyprexa 5 mg tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

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

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

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

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

Active substance
Olanzapin benzoate is an established active substance which is not described in the Ph.Eur.* or any other Pharamcopoeia. The drug substance is a yellow crystalline powder. It is sparingly soluble in N,N-dimethylformamide and methanol, slightly soluble in dimethyl sulfoxide, ethanol, acetone, dilute hydrochloric acid and chloroform, very slightly soluble in dichloromethane, ethyl acetate and isopropanol, practically insoluble in n-hexane, water and 1 mol/L of sodium hydroxide.
Different batches of Olanzapine benzoate were analysed by X-ray diffraction, IR spectrometry and differential thermal analysis. The test results indicate that the sample does not show polymorphism.

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 manufacturing process consists of four steps. Descriptions of the synthesis of the starting materials have been provided. A flow diagram of the manufacturing process has been provided, together with an extensive description of the manufacturing process.

Quality control of drug substance
The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 3 production-scale batches. The specification is acceptable for identification, appearance, clarity of solution, loss on drying, sulphated ash and heavy metals.

Stability of drug substance
Stability data on the active substance(s) have been provided for 3 batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (12 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. The photo stability results show no differences between the drug substance exposed to light and the dark control. Neither out of specifications nor trends have been observed.
Based on the data submitted, a re-test period of 2 years could be granted for the drug substance when stored in a dry and dark place. Although stability study results confirm that olanzapine benzoate is not

hygroscopic and that it is photostable the storage condition is used as a standard precaution during shipment and storage of the drug substance.
Some points for clarification remained related to potential impurities; which were solved by post-approval commitments.

** 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

Olanzapine Synthon 2,5 - are light yellow, round, biconvex tablets, debossed with "*OPN*" and "*2,5*" on one side and "*bza*" on the other side.
Olanzapine Synthon 5 - are light yellow, round, biconvex tablets, debossed with "*OPN*" and "*5*" on one side and "*bza*" on the other side.
Olanzapine Synthon 7.5 - are light yellow, round, biconvex tablets, debossed with "*OPN*" and "*7,5*" on one side and "*bza*" on the other side.
Olanzapine Synthon 10 - are light yellow, round, biconvex tablets, debossed with "*OPN*" and "*5*" on one side and "*bza*" on the other side.

The excipients are - calcium hydrogen phosphate (E341), cellulose microcrystalline (E460), magnesium stearate (E470), sodium starch glycolate type A.

The tablets are packed into Al/Al blisters. The contents of the four tablet formulations are dose proportional. The excipients and packaging are usual for this type of dosage form. . Also the 15 mg and the 20 mg tablets are dose proportional but not dose proportional with the other formulations.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The active substance in the drug product is olanzapine benzoate. Questions were raised on efficacy, safety and quality compared to a product with olanzapine. The applicant sufficiently discussed the acceptability of the benzoate form.
Dissolution profiles of all strengths have been provided. The profiles are similar. From the dissolution profiles which are included it can be concluded that the profiles are also similar to the biobatch, assuming that the same dissolution conditions are performed. The dissolution method is deemed to be acceptable in view of the fact that the product is an immediate release tablet and in view of the dissolution profile.

Container closure system
Two packaging types have been described: Al:Al blisters and bulk.
The tablets are packed in Al:Al blisters. The Al top foil consists of three layers: oPA/Al/PVC. The PVC is in contact with the drug product. The bottom foil consists of Al with a heat-seal lacquer. The heat-seal lacquer is also in contact with the product. It is declared that the lacquers comply with the directive 2002/72/EC.
The tablets (bulk) are packed in a LDPE bag which is closed. A desiccant bag is put on top of the LDPE bag and this package is put into a second LDPE bag. The two LDPE bags are then put into a large HDPE drum. The LDPE bag is transparent. Compliance of the LDPE with Ph. Eur. 3.1.4 is declared.
The drums are closed with a screw lid closure containing a natural rubber gasket.
The desiccant bag contains calcium aluminosilicate which is packed in a permeable polyester/polypropylene bag. It is stated that the desiccant bag is not in contact with the product.

Excipients
All ingredients used in Olanzapine Synthon tablets are well known and widely used as pharmaceutical excipients. The excipients used are sufficiently discussed (description, composition, application, incompatibilities and safety). All the excipients used in the Olanzapine (as benzoate) tablets are of the

quality of the Ph. Eur. Certificates of analysis, showing compliance with the specification, have been submitted for all excipients used.

Manufacturing process
The product is manufactured by a standard process. A flow diagram of the manufacturing process, including in process controls has been included. The manufacturing process consists of mixing of the constituents followed by direct compression and packaging.
Information on the blend properties (appearance, flowability, bulk density, tapped density, particle size and loss on drying) of the blends used has been submitted. The results are acceptable. Blend uniformity of the pre-compression blend has been studied for top, middle and bottom. The results are acceptable.

Quality control of drug product
The product specifications do cover all appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the specifications.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. The requirements for microbial contamination are in accordance with Ph. Eur. 5.1.4 and therefore acceptable.

Compatibility
It is stated that no incompatibilities between Olanzapine benzoate and the inactive ingredients dicalcium phosphate, microcrystalline cellulose, sodium starch glycolate – type A and magnesium stearate have not been found in literature, nor have been observed during the stability studies.

Stability tests on the finished product
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are drawn up.
The specification includes tests for appearance, appearance blister, seal integrity blister, hardness, friability (bulk only), disintegration time, water content, dissolution rate, identification (HPLC), assay, related substances and microbial contamination. As these parameters cover the stability indicating parameters, it is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. The proposed shelf-life of 24 months with the storage condition '*store in the original package in order to protect from moisture*' for the drug product is considered acceptable.
The shelf-life has been changed into 36 months by a post-appproval variation. (See *steps taken after finalisation of the initial procedure* table on page 11, variation NL/H/965/001-004/IB/016)

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
No excipients of animal and/or human origin are used in the tablets. A statement that the excipient magnesium stearate is of vegetable origin is enclosed.

II.2 Non clinical aspects

This product is a generic formulation of Zyprexa, which is available on the European market.
Since the Olanzapine Synthon 2,5/5/7,5/10/15/20 mg tablets contain olanzapine benzoate as active substance (instead of only olanzapine, which is the active substance for the innovator), the MAH has provided a non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology of olanzapine. This overview is considerd adequate.
The overview refers 69 publications up to year 2006. Olanzapine Synthon, which contains olanzapine benzoate is claimed to be a pharmaceutical alternative for Zyprexa 2,5, 5, 7,5, 10, 15 and 20 mg tablets (Ely Lilly) which contains olanzapine. To ensure that the safety profile of Synthon´s olanzapine benzoate was not different from other olanzapine containing products, non-clinical bridging studies have been performed. These studies comprised two repeated-dose toxicity studies in rats (14-day dose-range finding

study, 28-day bridging study) and two genotoxicity studies (Ames test, chromosomal aberration test). The results showed similar toxicity as that reported in the originator's registration studies. Considering that no new indications are added in this application, it is expected from the preclinical data that Olanzapine Synthon 2,5, 5, 7,5, 10, 15 and 20 mg tablets will substitute parts of the prescriptions of the currently marketed drug. No further preclinical data have been submitted. 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 olanzapine 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

Olanzapine 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 Olanzapine Synthon 5 mg tablets (Synthon, the Netherlands) is compared with the pharmacokinetic profile of the reference product Zyprexa 5 mg tablets (Eli Lilly, Germany).

Zyprexa tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

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

Bioequivalence study
A randomized, single dose, two-period-crossover, bioequivalence study was carried out under fasted conditions in 28 (24 + 4 alternates) healthy (14 male, 14 female) volunteers, aged 18-48 years. Nineteen of them were non smokers, and 9 subjects smoked 10 or less than 10 cigarettes a day. Each subject received a single dose (5 mg) of one of the 2 olanzapine formulations. The tablets were administered in solid form with 200 ml water after overnight fasting. Fasting was continued for 4 hrs after dosing. For each subject there were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Olanzapine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of olanzapine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results
One subjects was withdrawn from study due to adverse events. Twenty-seven subjects completed the study entirely, and as per protocol the first 24 subject were included in the analysis.

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

Treatment N = 24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	231 ± 80	251 ± 87	6.52 ± 2.04	4.0 (2.0 - 10.0)	35 ± 9
Reference	235 ± 86	255 ± 95	6.86 ± 1.91	5.0 (2.0 – 6.0)	34 ± 9
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	0.99 (0.95 – 1.04)	0.95 (0.90 – 0.99)	---	---
CV (%)	8.9	7.8	8.9	---	---

$AUC_{0-\infty}$ 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*

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 (active substance) under fasted conditions, it can be concluded that Olanzapine Synthon 5 mg tablets and the Zyprexa 5 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The 2.5, 7.5 and the 10 mg tablets are dose-proportional with the 5 mg tablet. The tablets have been manufactured by the same manufacturing process. In addition, olanzapine shows linear pharmacokinetics. Therefore the results obtained with the 5 mg strength can be extrapolated to the 2.5, 7.5 and 10 mg strengths.

Witdrawal of application for 15 mg and 20 mg strengths
Extrapolation of the bioequivalence results obtained with the 5 mg tablet to the 15 and 20 mg tablets was not possible in accordance with the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*. The 15 and 20 mg tablets are not dose-proportional with the lower tablet strengths. The ratio between amounts of active substance and excipients is not the same, and in addition, the 15 and 20 mg preparation do not contain a low concentration of active substance (less than 5%). Therefore it was concluded that the 15 mg and 20 mg tablets are not acceptable without prove of *in vivo* bioequivalence with the reference. In response, the applicant withdrew the application for the 15 and 20 mg tablet.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Olanzapine was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of olanzapine 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 innovator product has been authorised through the centralised procedure, and thus harmonised product information exists within the EU. The SPC has been harmonised with the innovator's SPC, with the exception of product particular sections and section 4.8 (description of frequency categories has been updated according to MEDRA).

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 leaflet for Olanzapine Synthon 5 mg tablets was used. A total of 22 participants were tested: 2 in a preliminary (pilot) round, to see if there are any major issues with the readability of the PIL, 10 in the first round of testing and 10 in the second round, after changes to the PIL have been made. Test results were obtained through interviewing.
Although some issues could have been described more elaborately in the report, the Member States are of opinion that the readability of the PIL, and hence also the appropriateness of the chosen format, design and layout, has been sufficiently demonstrated.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Olanzapine Synthon 2,5/5/7,5/10mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Zyprexa 2.5, 5, 7.5 and 10 mg coated tablets. The 15 mg and 20 mg tablets are not acceptable without demonstration of *in vivo* bioequivalence with the reference. Therefore, the application for the 15 and 20 mg tablet were withdrawn by the applicant. Zyprexa is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the innovator product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.
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 Olanzapine Synthon 2,5/5/7,5/10mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 October 2007.Olanzapine Synthon 2,5/5/7,5/10mg tablets is authorised in the Netherlands on 3 March 2009.

The first PSUR will cover the period from October 2007 to October 2008. Subsequent PSURs will cover 1 year until the 3-yearly cycle is accepted.

The date for the first renewal will be 23 October 2012.

There were no post-approval commitments made during the procedure.

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
MEDRA	Medical Dictionary for Regulatory Activities
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. All other manufacturing operations except batch release.	NL/H/965/ 001-004/IB/ 001	IB	2-1-2008	1-2-2008	Non-approval	N
Change in the name of the medicinal product.	NL/H/965/ 001-004/IB/ 002	IB	7-2-2008	8-3-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/965/ 001-004/IA/ 003	IA	25-1-2008	8-2-2008	Approval	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.	NL/H/965/ 001-004/IA/ 004	IA	25-1-2008	8-2-2008	Approval	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.	NL/H/965/ 001-004/IA/ 005	IA	25-1-2008	8-2-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/965/ 001-004/IA/ 006	IA	25-1-2008	8-2-2008	Approval	N
Change in batch size of the active substance or intermediate. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/965/ 001-004/IA/ 007	IA	4-1-2008	18-1-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/965/ 001-004/IB/ 008	IB	5-3-2008	4-4-2008	Approval	N
Change in the name of the medicinal product.	NL/H/965/ 001-004/IB/ 009	IB	5-3-2008	4-4-2008	Approval	N
Change in the name of the medicinal product.	NL/H/965/ 001-004/IB/ 010	IB	5-3-2008	4-4-2008	Approval	N
Change in the name of the medicinal product.	NL/H/965/ 001-004/IB/ 011	IB	15-9-2008	2-12-2008	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/965/ 001-004/IA/ 012	IA	5-11-2008	19-11-2008	Approval	N
Replacement or addition of a	NL/H/965/	IA	5-11-2008	19-11-2008	Approval	N

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.	001-004/IA/ 013					
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.	NL/H/965/ 001-004/IA/ 014	IA	25-6-2009	9-7-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.	NL/H/965/ 001-004/IA/ 015	IA	25-6-2009	9-7-2009	Approval	N
Change in shelf-life of the finished product as packaged for sale.	NL/H/965/ 001-004/IB/ 016	IB	30-7-2009	29-8-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/965/ 001-004/IB/ 017	IB	19-10-2009	18-11-2009	Approval	N
Amendment of the SPC and PIL to incorporate the wording of the PhVWP with respect to the risk of Venous Thromboemolism (VTE).	NL/H/965/ 001-004/II/ 018	II	21-1-2010	28-1-2010	Approval	N
Implementation of changes for which no new additional data are submitted by th MAH.	NL/H/965/ 001-004/IB/ 019	IB	4-2-2011	6-3-2011	Non-approval	N
Change in the (invented) name of the medicinal product.	NL/H/965/ 001-004/IB/ 020	IB	23-11-2010	23-12-2010	Approval	N
- Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product, secondary packaging site. - Change to batch release arrangements and quality control Procedure testing of the finished product. Replacement or addition of a manufacturer responsible for batch release, not including batch control/testing.	NL/H/965/ 001-004/IA/ 021/G	IA/G	14-12-2010	13-1-2011	Approval	N
Change in the (invented) name of the medicinal product for Nationally Authorised Products. Change of the name of the drug product in FI.	NL/H/965/ 001-004/IB/ 022	IB	18-1-2011	27-4-2011	Approval	N
Change of the product name in CZ.	NL/H/965/ 001-004/IB/ 023	IB	21-3-2011	24-6-2011	Approval	N