CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Venlafaxine PharOS 37.5 mg, 75 mg and 150 mg prolonged-release capsules, hard
PharOS – Pharmaceutical Oriented Services Ltd., Greece

venlafaxine (as hydrochloride)

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/2142/001-003/DC
Registration number in the Netherlands: RVG 108165-108167

5 December 2011

Pharmacotherapeutic group:	other antidepressants
ATC code:	N06AX16
Route of administration:	oral
Therapeutic indication:	Major depressive episodes; prevention of recurrence of major depressive episodes; generalised anxiety disorder; social anxiety disorder; panic disorder, with or without agoraphobia.
Prescription status:	prescription only
Date of authorisation in NL:	16 November 2011
Concerned Member States:	Decentralised procedure with DE, MT, PL
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 Venlafaxine PharOS 37.5 mg, 75 mg and 150 mg prolonged-release capsules, hard from PharOS – Pharmaceutical Oriented Services Ltd. The date of authorisation was on 16 November 2011 in the Netherlands.

The product is indicated for:
- treatment of major depressive episodes.
- for prevention of recurrence of major depressive episodes.
- treatment of generalised anxiety disorder.
- treatment of social anxiety disorder.
- treatment of panic disorder, with or without agoraphobia.

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

Venlafaxine is a structurally novel antidepressant that is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants.
Preclinical studies have shown that venlafaxine and its main metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine reuptake.
Studies in animals show that tricyclic antidepressants may reduce β-noradrenergic receptor responsiveness following chronic administration. In contrast, venlafaxine and its active metabolite reduce β-noradrenergic receptor responsiveness after both acute (single dose) and chronic administration. The clinical significance of this effect is not yet known. Venlafaxine and its main metabolite appear to be equipotent with respect to their overall action on neurotransmitter reuptake. In rats, venlafaxine has virtually no affinity for muscarinic cholinergic, H1-histamine or α1 receptors in vitro. Venlafaxine does not have any monoamine oxidase (MAO) inhibitory activity.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Efexor. The very first marketing authorisation in the EEA was obtained by Wyeth Pharmaceuticals for Efexor LP 37.5 mg capsules in France in May 1994. Efexor XR 37.5 mg, 75 mg and 150 mg (NL RVG 26661, 20862, 20863 respectively) have been registered in the Netherlands by Wyeth Pharmaceuticals since 1997 (75 mg and 150 mg) and 2001 (37.5 mg). In addition, reference is made to Efexor XR and Efexor Depot authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In Malta the application for the 37.5 mg strength is made according to article 10(3), hybrid application, as this strength is not available.

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 three bioequivalence studies in which the pharmacokinetic profile of the 150 mg product is compared with the pharmacokinetic profile of the reference product Trevilor Retard 150 mg capsules, 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 a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for 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 venlafaxine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to almost white powder, and is freely soluble in water. Venlafaxine HCl has one chiral centre. The drug substance is a racemate. The drug substance also shows polymorphism. Form B is manufactured.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP, with appropriate additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scaled batches.

Stability of drug substance
The active substance is stable for 24 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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

Medicinal Product

Composition
Venlafaxine PharOS 37.5 mg capsules are light grey opaque/peach opaque, size ‘3’ hard gelatin capsules having thick and thin radial circular band on the body in red ink and thick and thin radial circular band on the cap in red ink. The capsule is filled with 3 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.
Venlafaxine PharOS 75 mg capsules are peach opaque/peach opaque, size ‘1’ hard gelatin capsules having thick and thin radial circular band on the body in red ink and thick and thin radial circular band on the cap in red ink. The capsule is filled with 6 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.
Venlafaxine PharOS 150 mg capsules are dark orange/dark orange opaque, size ‘0’ hard gelatin capsules having thick and thin radial circular band on the body in white ink and thick and thin radial circular band on

the cap in white ink. The capsule is filled with 12 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each.

The prolonged release capsules are packed in blister packs of PVC/ACLAR film and Aluminum lidding foil.

The excipients are:
Core - microcrystalline cellulose (Avicel PH 102), povidone (Plasdone K-90 D), talc, colloidal anhydrous silica, magnesium stearate.
Coating - ethyl cellulose (Ethocel 7 CP STD Premium FP), copovidone (Plasdone S-630)
37.5 mg capsule - black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), gelatin, shellac, propylene glycol, strong ammonia solution
75 mg capsule - black iron oxide (E172), red iron oxide (E172), titanium dioxide (E171), gelatin, shellac, propylene glycol, strong ammonia solution
150 mg capsule - Brilliant Blue FCF (E133), Allura Red AC (E129), Sunset Yellow FCF (E110), titanium dioxide (E171), gelatin, shellac, povidone, propylene glycol, sodium hydroxide.

The three different strengths are fully dose proportional.

Pharmaceutical development
The capsules are of size 3, 1 and 0, and the drug product is composed of 3 to 12 extended release mini-tablets packed into a capsule shell. A coating level of 6% is also applied for the batches used in the stability studies. The chosen excipients are widely used in pharmaceutical preparations. The different functions of the excipients are well described. Because the innovator product and the test product are manufactured using different excipients, the similarity was based on the dissolution profile.
The dissolution profiles of several innovator products were determined. It was shown that the current formulation has similar dissolution profiles in different dissolution media. The pharmaceutical development has been adequately performed and explained.

Manufacturing process
The manufacture of the drug products comprises of manufacture of core mini tablets of 12.5 mg and its coating with release controlling polymers. The coated tablets are then filled in capsules.
Appropriate in-process controls are applied throughout the manufacture of tablets to ensure the tablets for its acceptable physical characteristics. All the critical process steps / parameters, which can affect the quality of the product, were studied and optimized. In general the manufacturing of the drug product has been adequately described.
An adequate process validation was performed. Validation studies have been performed on three batches of mini tablets. The filling process of the 75 mg and 150 mg strengths has been validated using three full-scale batches of each strength. The MAH committed to validate the filling process of the first three full industrial batches of 37.5 mg capsules.

Control of excipients
The excipients of the venlafaxine prolonged release capsules comply with Ph.Eur. or Directive 95/45/EC, except for ethanol denatured which complies with in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification by HPLC and UV, weight of 20 capsules, uniformity of mass, uniformity of dosage units, loss on drying, assay of venlafaxine, dissolution, related substances, residual solvents, XRD and microbiological quality. The test parameters included are common and acceptable for prolonged release capsules. The dissolution limits has been tightened upon request of the RMS, the other specification limits are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot scaled batch sizes, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided three pilot scaled batches of each strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored PVC/Aclar-Alu packaging.
Water content increases slightly and all other parameters remain relatively stable. Photostability studies were performed on 600 mini tablets, crushed into a fine powder and spread in a Petri dish. The powder was subjected to 1.2 million lux. No significant changes were observed.
Based on the stability data, the approved shelf life is 3 years, when stored in original package below 25°C.

The MAH committed to perform stability studies on commercial-scale 37.5 mg batches as per frequency defined in the stability protocol (accelerated 6 months, long term 36 months). Also a commitment was made to subject the first three commercial batches of the 37.5 mg capsules to long term stability studies as per stability protocol upon manufacture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is the only excipient of animal origin. CEPs for the gelatin used in the capsule shells have been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Efexor XR, 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 venlafaxine 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

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

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the test product Venlafaxine PharOS 150 mg (PharOs, Greece) is compared with the pharmacokinetic profile of the reference product Trevilor Retard 150 mg capsules (Wyeth GmbH, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I – single-dose, fasted, 150 mg
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects. Each subject received a single dose (150 mg) of one of the 2 venlafaxine formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 19 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Analytical/statistical methods

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

Results
Two subjects left the study because of positive testing of the use of benzodiazepines and withdrawal for personal reasons. Forty-two subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=42	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4466.0 ± 2412.4	4649.4 ± 2603.4	214.7 ± 70.2	7.0	9.3 ± 2.4
Reference	4047.5 ± 2178.8	4139.3 ± 2275.1	205.5 ± 58.7	7.0	9.3 ± 2.8
***Ratio (90% CI)**	1.09 (1.02-1.15)	1.08 (1.02-1.15)	1.02 (0.96-1.09)	-	-
CV (%)	16.5	16.5	17.2	**-**	**-**

$AUC_{0-\infty}$ 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 venlafaxine under fasted conditions, it can be concluded that Venlafaxine PharOS 150 mg and Trevilor Retard 150 mg prolonged release capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – single-dose, fed, 150 mg
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 44 healthy male subjects. A high fat breakfast of approximately 1000 Calories was served before the products were administered. More than 50% of the calories consisted of fat (60 gram fat, 70 gram carbohydrates and 39 gram of protein). Each subject received a single dose (150 mg) of one of the 2 venlafaxine formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 19 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

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

Results

One subject was withdrawn because of a positive alcohol test at entry for period II. Forty-three subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=43	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3158.8 ± 2027.0	3596.6 ± 2282.7	153.1 ± 51.3	7.5	11.5 ± 6.9
Reference	3304.6 ± 2017.2	3635.1 ± 2637.7	167.7 ± 52.5	5.5	10.5 ± 4.8
***Ratio (90% CI)**	0.94 (0.88-1.01)	1.00 (0.94-1.07)	0.90 (0.83-0.98)	-	-
CV (%)	19.5	18.5	23.6	**-**	**-**

$AUC_{0-\infty}$ 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 venlafaxine under fed conditions, it can be concluded that Venlafaxine PharOS 150 mg and Trevilor Retard 150 mg prolonged release capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study III – multiple-dose, fed, 150 mg

Design

A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects. A high fat breakfast of approximately 1000 Calories was served before the products were administered for 5 consecutive days. More than 50% of the calories consisted of fat (60 gram fat, 70 gram carbohydrates and 39 gram of protein). Each subject received a single dose (150 mg) of one of the 2 venlafaxine formulations. The tablet was orally administered with 240 ml water. There was a washout period of at least 10 days between the last dose of period I and the first dose of period II.

Pre-dose blood samples were collected one hour before dosing on days 1, 2, 3, 4 and 5. Post-dose blood samples were collected on day 5 at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 16 and 24 hours after dosing.

Analytical/statistical methods

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

Results

Two subjects were withdrawn from the study as they tested positive for benzodiazepines in check-in for period II. Thirty-four subjects completed both periods and were included in the final pharmacokinetic and statistical analysis.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=34	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	3243.6 ± 2327.2	244.8 ± 170.7	66.1 ± 57.7	140 ± 65.8
Reference	3240.8 ± 2107.9	232.9 ± 134.8	65.7 ± 60.4	138.1 ± 34.2
***Ratio (90% CI)**	0.96 (0.91-1.02)	0.96 (0.86-1.08)	1.01 (0.93-1.10)	--
CV (%)	14.1	28.7	20.3	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index

The 90% confidence intervals calculated for AUC_{0-t}, C_{min} 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 venlafaxine at steady state under fed conditions, it can be concluded that Venlafaxine PharOS 150 mg and Trevilor Retard 150 mg prolonged release capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Food effect
Bioequivalence was demonstrated under fed, fasted and multiple-dose conditions as is required for prolonged release capsules to exclude dose dumping effect of food. As could be expected based on SPC of the innovator product, food had no significant effect on the absolute bioavailability of venlafaxine. The prolonged release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet.

Extrapolation to other strengths
According to the guideline, only the highest strength, the 150 mg capsule, has been tested. Extrapolation to the lower strengths (37.5 and 75 mg) is possible as the following criteria according the EMA guideline on modified release products are fulfilled:

a) The pharmacokinetics of venlafaxine are linear;
b) The qualitative composition of the capsules is the same;
c) The ratio between active substance and the excipients in all strengths is the same;
d) The dissolution rate of the highest strength of the product *in vitro* is similar to those of the lower strengths, and the dissolution rate of all the strengths of the test product *in vitro* is similar to the dissolution rates of the corresponding strengths of the reference product. This was tested at different pH values.

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
Venlafaxine was first approved in September 1993, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of venlafaxine 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 European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with those accepted for other venlafaxine containing products.
Readability test
The package leaflet has not been evaluated via a user consultation study. As the PL has been fully adapted to a user-friendly PL, a waiver was granted for user testing.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Venlafaxine PharOS 37.5 mg, 75 mg and 150 mg prolonged-release capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Efexor XR 37.5 mg, 75 mg and 150 mg capsules. Efexor XR is a well-known medicinal product with an established favourable efficacy and safety profile.

Venlafaxine PharOs is a prolonged release, multiple unit formulation. According to the guideline CPMP/EWP/280/96, three studies under fasting, fed and multiple dose conditions are required for prolonged release formulations at the highest strength (*in casu* 150 mg). 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 in the agreed templates and consistent with that of the reference product.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Venlafaxine PharOS 37.5 mg, 75 mg and 150 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 September 2011. Venlafaxine PharOS 37.5 mg, 75 mg and 150 mg prolonged-release capsules were authorised in the Netherlands on 16 November 2011.

A European harmonised birth date has been allocated (23 September 1993) and subsequently the first data lock point for venlafaxine is 31 May 2012. The first PSUR will cover the period from April 2009 to May 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: January 2016

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

Quality - medicinal product

- The MAH committed to validate the filling process for commercial-scale batches of 37.5 mg capsules once manufactured and a validation report shall be provided to the relevant Authorities.
- The MAH committed to perform stability studies on commercial-scale 37.5 mg batches as per frequency defined in the stability protocol (accelerated 6 months, long term 36 months).
- The MAH committed to subject the first three commercial batches of the 37.5 mg capsules to long term stability studies as per stability protocol upon manufacture.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached