PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Venlafaxine HCl XR 75 mg and 150 mg,
prolonged-release capsules, hard
Valpharma International S.p.A., Italy

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. It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 33857-33858

30 August 2010

Pharmacotherapeutic group: other antidepressants
ATC code: N06AX16
Route of administration: oral
Therapeutic indication: major depressive episodes; social anxiety disorder
Prescription status: prescription only
Date of authorisation in NL: 12 November 2008
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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Venlafaxine HCl XR 75 mg and 150 mg prolonged-release capsules, hard from Valpharma International S.p.A. The date of authorisation was on 12 November 2008 in the Netherlands.

The product is indicated for:
- treatment of major depressive episodes.
- treatment of social anxiety disorder.

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 national procedure concerns a generic application claiming essential similarity with the innovator products Efexor XR 75 mg and 150 mg (NL License RVG 20862-20863) which have been registered in the Netherlands by Wyeth Pharmaceuticals since 4 December 1997.

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

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the 150 mg product is compared with the pharmacokinetic profile of the reference product Efexor XR 150 mg capsules, registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

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

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

II.1 Quality aspects

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

Active substance
The active substance is venlafaxine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to off-white crystalline powder, which is very soluble in water, and freely soluble in alcohol and chloroform. It has one chiral centre, but is used as a racemic mixture. Only one polymorphic form is used.

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 Ph.Eur., with additional requirements for assay and chloride. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production-scale batches and one pilot-scale batch.

Stability of drug substance
Stability data were submitted on 4 batches of active substance stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months). Based on the results, the proposed re-test period of 4 years, as well as the storage condition ‘store protected from light’ are acceptable.

* 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 HCl XR 75 mg is a hard gelatine size 2 capsule, with white opaque cap and body, containing white or whitish pellets.
Venlafaxine HCl XR 150 mg is a hard gelatine size 0. capsule, with natural transparent cap and body, containing white or whitish pellets.

The 75 and 150 mg capsules are fully dose proportional.

The hard capsules are packed in PVC/PVDC/aluminium blisters.

The excipients are: sugar spheres (sucrose and maize starch), stearic acid (E570), ethylcellulose (E462), talc (E553b), titanium dioxide (E171) and gelatin (capsules).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Sugar spheres are used as inert cores; ethylcellulose and stearic acid are used as delaying agents and talc is used as an anti-static agent and for lubrication. Several compositions were tested, which differed in release-properties. A comparison of dissolution data of the UK products and the Dutch registered products is provided. The dissolution profiles are very similar. The proposed product and the reference product showed comparable dissolution characteristics in four different media. The pharmaceutical development of the product has been adequately performed. A bioequivalence study has been performed with the proposed composition.

Manufacturing process
The sugar spheres are coated with the active substance, followed by a coating that provides the sustained release properties. The coated pellets are then filled into gelatine capsules. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using a non-standard process. Process validation data on the product has been presented for three production-scale batches of coated pellets which resulted in several batches of capsules.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification (active substance, chloride and titanium dioxide), uniformity of dosage units, average mass if contents, uniformity of mass, dissolution, impurities, residual solvents, and microbiology. The release and shelf-life criteria are identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two production-scale batches of the 75 mg capsules and of one pilot-scale and two production scale batches of the 150 mg capsules, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on one pilot-scale and two production-scale batches of each capsule strength. These batches were stored at 25°C/60% RH, 30°C/65% RH, 30°C and 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed Al/PVDC-PVC/PVDC blisters and in bulk packs. Data is available up to 36 months of one pilot batch of 150 mg, one production batch of 75 mg and one production batch of 150 mg capsules. These production batches were derived of one common batch of coated sugar spheres and should therefore be considered one batch with regards to the most critical aspect of the manufacturing process. Data is available up to 12 months of the pilot-scale batch of the 75 mg capsules. Sufficient stability data has been submitted to grant the proposed shelf life of 3 years. The applicable storage condition is 'store in the original packaging in order to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatine is of animal origin and all other excipients are of vegetable or mineral origin. 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 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 HCl XR 150 mg (Valpharma International S.p.A., Italy) with is compared with the pharmacokinetic profile of the reference product Efexor XR 150 mg, prolonged-release capsules (Wyeth, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence studies 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, two-way crossover bioequivalence study was carried out under fasted conditions in 42 healthy subjects (8 males/34 females), aged 18-54 years. Each subject received a single dose (150 mg) of one of the 2 venlafaxine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 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
Five subjects were withdrawn from the study, four of them because of vomiting, and one for personal reasons. Thirty-seven subjects completed the study entirely and were included in the analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) ng.h/ml</th>
<th>( \text{AUC}_{0-\infty} ) ng.h/ml</th>
<th>( C_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
<th>( t_{1/2} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1510 ± 907</td>
<td>1640 ± 1053</td>
<td>104 ± 47.7</td>
<td>5.5 (4-7)</td>
<td>8.82 ± 1.7</td>
</tr>
<tr>
<td>Reference</td>
<td>1483 ± 961</td>
<td>1702 ± 1344</td>
<td>96.3 ± 43.5</td>
<td>6.5 (5-12)</td>
<td>9.82 ± 2.4</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.03 (0.98-1.09)</td>
<td>1.00 (0.95-1.06)</td>
<td>1.08 (1.03-1.14)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>13</td>
<td>15</td>
<td>13</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) 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 HCl XR 150 mg and Efexor XR 150 mg prolonged-release capsules are bioequivalent with respect to rate and extent of absorption, and fulfill 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, two-way crossover, laboratory-blind bioequivalence study was carried out under fed conditions in 42 healthy subjects (11 males/31 females), aged 18-51 years. Each subject received a single dose (150 mg) of one of the 2 venlafaxine formulations. The capsule was orally administered with 240 ml water within 30 minutes after a high-fat breakfast (800-1000 calories). There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 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 withdrew from the study for personal reasons. The remaining 41 subjects completed the study entirely and were included in the analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-4} ) ng.h/ml</th>
<th>( \text{AUC}_{0-\infty} ) ng.h/ml</th>
<th>( C_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
<th>( t_{1/2} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2184 ± 1613</td>
<td>2427 ± 1996</td>
<td>148 ± 75.5</td>
<td>6.5 (5-16)</td>
<td>7.13 ± 2.7</td>
</tr>
<tr>
<td>Reference</td>
<td>1963 ± 1417</td>
<td>2317 ± 1909</td>
<td>131 ± 64.6</td>
<td>5.5 (3-9)</td>
<td>10.4 ± 3.1</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.10 (1.02-1.18)</td>
<td>1.05 (0.97-1.13)</td>
<td>1.12 (1.03-1.22)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>20</td>
<td>20</td>
<td>23</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*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_{\text{max}}*, maximum plasma concentration

\( t_{\text{max}} \), 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 $C_{\text{max}}$ 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 HCl XR 150 mg and Efexor XR 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, fasted, 150 mg

**Design**
A multiple-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 42 healthy subjects (27 males/15 females), aged 18-53 years. Each subject received a dose of one of the venlafaxine formulations once daily for four following days (4 x 150 mg). Plasma sampling for the curve took place at Day 4, under fasted conditions. For each subject there were 2 dosing periods, separated by a washout period of 8 days.

One sample was taken at Day 1, before any drug intake. Trough samples were taken at Day 2, 3 and 4, immediately before drug intake. At Day 4, blood samples were taken at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 12, 16 and 24 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**
Three subjects were withdrawn from the study; one because of an upper respiratory tract infection, and two because of nausea and coughing. Thirty-nine subjects completed the study entirely and were included in the analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range)) of venlafaxine at day 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ ng.h/ml</th>
<th>$C_{\text{max-ss}}$ ng.h/ml</th>
<th>$C_{\text{min-ss}}$ ng/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$t_{\frac{1}{2}}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2055 ± 1108</td>
<td>149 ± 62.8</td>
<td>38.0 ± 28.9</td>
<td>5.5 (4.5-8)</td>
<td>--</td>
</tr>
<tr>
<td>Reference</td>
<td>1974 ± 1223</td>
<td>140 ± 64.3</td>
<td>34.1 25.4</td>
<td>5.5 (4.5-8)</td>
<td>--</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

| *Ratio (90% CI) | 1.07 (1.02-1.13) | 1.08 (1.02-1.14) | 0.89 (0.83-0.95) | -- | -- |

| CV (%) | 14 | 14 | 17 | -- | -- |

$AUC_{0-\infty}$ 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

$C_{\text{max}}$ maximum plasma concentration

$t_{\text{max}}$ time for maximum concentration

$t_{\frac{1}{2}}$ half-life

*ln-transformed values

The 90% confidence intervals calculated for $AUC_{0-t}$, $C_{\text{min}}$ and $C_{\text{max}}$ 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 in a multi-dose study under fasted conditions, it can be concluded that Venlafaxine HCl XR 150 mg and Efexor XR 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.

In addition to the results provided above, the MAH submitted analytical data on the active metabolite O-desmethylvenlafaxine. These data were regarded as supportive.

**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 the 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 75 mg capsules**

The results of the bioequivalence studies with the 150 mg strength can be extrapolated to the 75 mg capsules, as following criteria according the EMA guideline on modified release products are fulfilled:

a) the compositions of the lower strength are proportional to that of the highest strength,

b) the formulations contain identical beads or pellets,

c) the active compound show linear kinetics,

d) the dissolution rate of the highest strength of the product *in vitro* is similar to that of the lower strength.

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**

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. 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 national procedure is in accordance with that accepted for the reference product Efexor XR.

**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 test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed. Moreover, the PIL has been brought in line with the approved, user tested PIL for Efexor.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Venlafaxine HCl XR 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, package leaflet and labelling are in the agreed templates and are in agreement with other venlafaxine containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Venlafaxine HCl XR 75 mg and 150 mg, prolonged-release capsules, hard were authorised in the Netherlands on 12 November 2008.

There were no post-approval commitments made during the procedure.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PIL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SS</td>
<td>Steady state</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>Half-life</td>
</tr>
<tr>
<td>$t_{max}$</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
</tr>
</tbody>
</table>
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of new batch release site for the finished product.</td>
<td>--</td>
<td>IA</td>
<td>2-2-2009</td>
<td>5-2-2009</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Addition of new manufacturing site for the finished product.</td>
<td>--</td>
<td>IB</td>
<td>2-2-2009</td>
<td>18-3-2009</td>
<td>Approval</td>
<td>N</td>
</tr>
</tbody>
</table>