PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Venlafaxine Docpharma 37.5 mg, 75 mg and 150 mg, prolonged release capsules, hard
DOCPHARMA N.V., Belgium

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/1152/001-003/DC
Registration number in the Netherlands: RVG 100611-100613

3 June 2010

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 disorders, with or without agoraphobia.

Prescription status: prescription only
Date of authorisation in NL: 12 April 2010
Concerned Member States: Decentralised procedure with BE, FR, IT, LU
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 Docpharma 37.5 mg, 75 mg and 150 mg prolonged release capsules, hard from DOCPHARMA N.V. The date of authorisation was on 12 April 2010 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 products Efexor XR 37.5 mg, 75 mg and 150 mg (NL RVG 26661, 20862, 20863 respectively) which 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.

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. 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 almost white powder, and is freely soluble in methanol and water, soluble in anhydrous ethanol and slightly soluble or practically insoluble in acetone. Venlafaxine has one chiral centre but is manufactured as a racemate. Only one polymorphic is used.

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.

Manufacturing process
Venlafaxine hydrochloride is prepared via a three-stage synthesis. The drug substance has been adequately characterized. The solvents used during the manufacturing process are adequately limited in the drug substance specifications.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and with an adequate addition of specifications for solid phase identification by XRD and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data has been obtained for three commercial-scale batches during storage at 25°C/60%RH (24 months) and 40°C/75% RH (6 months). The drug substance was adequately stored. The solid drug substance can be regarded as stable and a re-test period of 24 months, when stored in the original package, was granted. The study demonstrated that there is no change in polymorphic form.

* 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 Docpharma 37.5 mg is a light grey opaque/peach opaque capsule with a red band on the body and cap, containing venlafaxine hydrochloride 42.45 mg equivalent to 37.5 mg venlafaxine. The capsule contains three round, biconvex, film-coated white to off-white mini tablets of 12.5 mg drug substance as venlafaxine each.

Venlafaxine Docpharma 75 mg is a peach opaque/peach opaque capsule with a red band on the body and cap, containing venlafaxine hydrochloride 84.9 mg equivalent to 75 mg venlafaxine. The capsule contains six round, biconvex, film-coated white to off-white mini tablets of 12.5 mg drug substance as venlafaxine each.
Venlafaxine Docpharma 150 mg is a dark orange/dark orange capsule with a white band on the body and cap, containing venlafaxine hydrochloride 169.8 mg equivalent to 150 mg venlafaxine. The capsule contains twelve round, biconvex, film-coated white to off-white mini tablets of 12.5 mg drug substance as venlafaxine each.

The three different strengths are fully dose proportional.

The prolonged release capsules are packed in Alu/PVC/ACLAR/Alu blister packs.

The excipients are:
Contents of capsule
Microcrystalline Cellulose (E460)
Povidone
Talc (E553b)
Silica, Colloidal Anhydrous (E551)
Magnesium Stearate (E572)
Ethyl Cellulose
Copovidone

Capsule shell
Titanium dioxide (E171)
Gelatin (37.5 and 75 mg)
Black and Red iron oxide (E172) (37.5 and 75 mg)
Red ink SB-1033 (37.5 and 75 mg)
Yellow iron oxide (37.5 mg)
Brilliant Blue FCF (E133) (150 mg)
Allura Red AC (E129) (150 mg)
Sunset Yellow FCF (E110) (150 mg)
White Ink SB-0007P (150 mg)

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 37.5 mg, 75 mg and 150 mg drug products comprises of manufacture of core mini-tablets of 12.5 mg and its coating with a 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 data on production-scale batch size was provided.

Control of excipients
The excipients comply with the requirements for their respective Ph.Eur. monographs. 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 weight, 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.

Three commercial full-scale batches of mini tablets have been submitted. These tablets were used to produce the full-scale batches for the different strengths of capsules for batch analysis. All batches comply with the proposed set of specifications.

Stability of drug product
Two pilot scaled batches of each strength were tested for 24 months long term (25°C/60%RH) and one batch of each strength was tested for 18 months long term. No significant changes were observed. The water content increases during storage under both conditions, but remains well within the end of shelf life specifications. The values for dissolution remain relatively stable throughout the storage period. No increase in any of the impurities is seen. A shelf-life of 24 months was therefore granted. No specific storage conditions are necessary.

A photostability study was performed in accordance with the ICH guideline up to 1.2 million Lux hours and integrated near UV range of 200 watts hours/square meter. From the study it can be concluded that the product is photostable. The photostability study has been performed on the powder, which is acceptable. Influence of the capsule shells on the powder during the photostress is not expected.

The MAH committed to perform stability studies on the first three commercial batches of each pack of the 37.5 mg, 75 mg and 150 mg product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A certificates of suitability issued by the EDQM has been provided for the gelatine used in the capsule shells. The magnesium stearate used is of 100% vegetable origin.

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 Docpharma 150 mg (DOCPHARMA N.V., Belgium) 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\text{max} (median, range)) of venlafaxine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=42</th>
<th>AUC\text{0-t} ng.h/ml</th>
<th>AUC\text{0-∞} ng.h/ml</th>
<th>C\text{max} ng/ml</th>
<th>t\text{max} h</th>
<th>t\text{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>4649.4 ± 2603.4</td>
<td>4466.0 ± 2412.4</td>
<td>214.7 ± 70.2</td>
<td>7.0</td>
<td>9.3 ± 2.4</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>4139.3 ± 2275.1</td>
<td>4047.5 ± 2178.8</td>
<td>205.5 ± 58.7</td>
<td>7.0</td>
<td>9.3 ± 2.8</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.09 (1.02-1.15)</td>
<td>1.08 (1.02-1.15)</td>
<td>1.02 (0.96-1.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AUC\text{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC\text{0-∞} area under the plasma concentration-time curve from time zero to infinity
C\text{max} maximum plasma concentration
t\text{max} time for maximum concentration
t\text{1/2} half-life

*ln-transformed values

The 90% confidence intervals calculated for AUC\text{0-t}, AUC\text{0-∞} 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 Docpharma 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.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/ml)</th>
<th>AUC_{0-\infty} (ng.h/ml)</th>
<th>C_{max} (ng/ml)</th>
<th>t_{max} (h)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3158.8 ± 2027.0</td>
<td>3596.6 ± 2282.7</td>
<td>153.1 ± 51.3</td>
<td>7.5</td>
<td>11.5 ± 6.9</td>
</tr>
<tr>
<td>Reference</td>
<td>3304.6 ± 2017.2</td>
<td>3635.1 ± 2637.7</td>
<td>167.7 ± 52.5</td>
<td>5.5</td>
<td>10.5 ± 4.8</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.94 (0.88-1.01)</td>
<td>1.00 (0.94-1.07)</td>
<td>0.90 (0.83-0.98)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CV (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
AUC_{0-\infty} area under the plasma concentration-time curve from time zero to infinity
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 Docpharma 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. 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 (non-transformed values; arithmetic mean ± SD, t_max (median, range)) of venlafaxine under fed conditions, at day 5.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/ml)</th>
<th>C_{min} (ng/ml)</th>
<th>C_{max} (ng/ml)</th>
<th>t_{max} (h)</th>
<th>t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>3243.6 ± 2327.2</td>
<td>66.1 ± 57.7</td>
<td>244.8 ± 170.7</td>
<td>102.0</td>
<td>-</td>
</tr>
<tr>
<td>Reference</td>
<td>3240.8 ± 2107.9</td>
<td>65.7 ± 60.4</td>
<td>232.9 ± 134.8</td>
<td>101.0</td>
<td>-</td>
</tr>
<tr>
<td><em>Ratio (90% CI)</em></td>
<td>0.96 (0.91-1.02)</td>
<td>1.01 (0.93-1.10)</td>
<td>0.96 (0.86-1.08)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CV (%)</td>
<td>14.1</td>
<td>20.2</td>
<td>28.7</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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

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 in a multi-dose study under fed conditions, it can be concluded that Venlafaxine Docpharma 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 EMEA 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 in water, at pH 1.0, 4.5 and 6.8.

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 postauthorisation 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 SPC has been adapted in accordance with the SPC as issued by the CHMP through an article 30 referral for Efexor depot.

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 a pilot test with 2 participants, followed by two rounds with 10 participants each. No revisions were made after the first round, since the results of the first round were sufficient. Diagnostic testing was performed and questions (18 open questions in total) were asked about all parts of the leaflet.
The report is of good quality and the results show that the PIL fulfils the criteria as set in the Readability Guideline.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Venlafaxine Docpharma 37.5 mg, 75 mg and 150 mg prolonged release capsules 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 Docpharma 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 committed to confirm that systems and services are in place to ensure compliance with their pharmacovigilance obligations (see below).

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 Docpharma 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 8 October 2008. Venlafaxine Docpharma 37.5 mg, 75 mg and 150 mg prolonged release capsules were authorised in the Netherlands on 12 April 2010.

A European harmonised birth date has been allocated (23 September 1993) and subsequently the first data lock point for venlafaxine is 31 May 2009. The first PSUR will cover the period from October 2008 to May 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 1 February 2013.

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

Quality - medicinal product
- The MAH committed to perform stability studies on the first three commercial batches of each pack of the 37.5 mg, 75 mg and 150 mg product.

Pharmacovigilance system
- The MAH committed to fulfill the following pharmacovigilance requirements before the product is placed on the market:
  o No description of the back-up procedure to apply in the absence of the Qualified Person for Pharmacovigilance (QPPV) was provided. The links with other organisations should be described more extensively.
  o A copy of the registration, of the QPPV, with the EudraVigilance system and identification of the process used for electronic reporting to the Competent Authorities was not yet provided.
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
Cmax   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
QPPV   Qualified Person for Pharmacovigilance
SD     Standard Deviation
SPC    Summary of Product Characteristics
t½     Half-life
tmax   Time for maximum concentration
TSE    Transmissible Spongiform Encephalopathy
USP    Pharmacopoeia in the United States
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