PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Venfalex XR 37.5 mg, prolonged release capsules, hard
Venfalex XR 75 mg, prolonged release capsules, hard
Venfalex XR 150 mg, prolonged release capsules, hard

Alfred Tiefenbacher (GmbH & Co. KG), Germany

venlafaxine

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/927/01-03/MR
Registration number in the Netherlands: RVG 31854, 31855, 31856

12 March 2008

Pharmacotherapeutic group:	Psychoanaleptics, antidepressants, other antidepressants
ATC code:	N06AX16
Route of administration:	oral
Therapeutic indication:	major depressive episodes, short-term treatment of generalised anxiety disorder, short-term treatment of social anxiety disorder/ social phobia, and treatment of panic disorders, with or without agoraphobia.
Prescription status:	prescription only
Date of authorisation in NL:	12 July 2006
Concerned Member States:	CY, CZ, EE, EL, LT, LV, SK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Venfalex XR 37.5, 75 and 150 mg prolonged release capsules, hard, from Alfred Tiefenbacher (GmbH & Co. KG). The first date of authorisation was on 12 July 2006 in the Netherlands. The product is indicated for the treatment of major depressive episodes, short-term treatment of generalised anxiety disorder, short-term treatment of social anxiety disorder/ social phobia, and treatment of panic disorders, with or without agoraphobia.

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

Venlafaxine is an antidepressant, which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants (e.g. SSRI). Venlafaxine is a racemate with two active enantiomers.
The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethyl-venlafaxine, are potent inhibitors of serotonin and noradrenalin reuptake. Venlafaxine inhibits also weakly dopamine uptake. Studies in animals show that tricyclic antidepressants may reduce β-adrenergic responsiveness following chronic administration. In contrast, venlafaxine and O-desmethyl-venlafaxine reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and O-desmethyl-venlafaxine are very similar with respect to their overall action on neurotransmitter reuptake.
Venlafaxine has virtually no affinity for rat brain muscarinic cholinergic, H1-histaminergic or α1-adrenergic receptors in vitro. Pharmacological activity at these receptors may be related to various side effects seen with other antidepressant drugs, such as anticholinergic, sedative and cardiovascular side effects. Venlafaxine does not possess monoamine oxidase inhibitory activity.

This application concerns a generic application claiming essential similarity with the Dutch innovator product Efexor XL 37.5, 75 and 150 mg prolonged release capsules, containing respectively 37.50, 75.00 and 150.00 mg venlafaxine, which have been registered in the European Union since 1994 by Wyeth Pharmaceuticals/NL (Dutch MA-numbers RVG 20862, 20863 and 26661). In addition, reference is made to Efexor authorisations in the individual member states (reference product). However, not all indications are as such accepted in all member states. To harmonise the indications and other aspects of the SPC an article 30 referral procedure for the innovator Efexor XL has been initiated in the CHMP.

The marketing authorisation is granted in the Netherlands based on article 10(1) of Directive 2001/83/EC. In all concerned member states the legal basis for the 75 and 150 mg formulation is article 10(1). In CZ, EE, LT, LV, and SK the legal basis for the 37.5 mg strength is also article 10(1), whereas in CY and EL the legal basis is article 10(3), a so called hybrid application. These deviations are made, because of the absence of the 37.5 mg strength for the innovator in CY and EL. However, since the strengths applied for are in agreement with the posology, this is deemed acceptable.

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 two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Efexor XL 75 mg prolonged release capsules, hard, by Wyeth Laboratories UK, registered in the United Kingdom. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

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

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for 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 and excipients
The active substance is venlafaxine (as hydrochloride), an established active substance described in the European Pharmacopoeia (Ph.Eur.). 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. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 3 production batches.

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.

Stability data on the active substance have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over a period of 24 months without special storage conditions. On the basis of the data submitted, a retest period of 2 years was granted.

The excipients (including sugar spheres) comply with the relevant Ph.Eur. monographs, except for the prolonged release coating Surelease E-7-7050 and hard gelatine capsule shells, for which adequate in-house specifications apply.

Medicinal Product

Composition
Venfalex XR, 37.5, 75 and 150 mg prolonged release capsules contain as active ingredient venlafaxine (37.50, 75.00 and 150.00 mg) corresponding to 42.435, 84.870 and 169.740 mg of venfalaxine hydrochloride, respectively. The three strengths are dose-proportional. Venfalex prolonged release capsules consist of encapsulated beads (multiple unit capsule formulation), which release venlafaxine by diffusion through a slowly dissolving coating mechanism.

Venfalex XR 37.5 mg, prolonged release capsules, are white to off-white pellets filled in hard gelatin capsule shells size "3" with orange cap and clear transparent body.
Venfalex XR 75 mg, prolonged release capsules, are white to off-white pellets filled in hard gelatin capsule shells size "1" with yellow cap and clear transparent body.
Venfalex XR 150 mg, prolonged release capsules, are white to off-white pellets filled in hard gelatin capsule shells size "o" with buff cap and clear transparent body.

The capsules are packed in PVC/Aluminium blisters or HDPE container with HDPE screw cap.

The excipients for all strengths are: sugar spheres (contains sucrose), ethyl cellulose (E462), hydroxypropylcellulose, hypromellose (E464), talc (E553b), dibutyl sebacate, oleic acid, colloidal anhydrous silica, gelatin and sodium lauryl sulphate.

Differences in pigments between the different strengths are present in the capsule shell.
For the capsule cap of the 37.5 mg strength: ponceau 4R (E124), quinoline yellow (E104) and titanium dioxide (E171).
For the capsule cap of the 75 mg strength: sunset yellow (E110), quinoline yellow (E104) and titanium dioxide (E171).
For the capsule cap of the 150 mg strength: sunset yellow (E110), quinoline yellow (E104), patent blue (E131) and titanium dioxide (E171).

The used excipients are well known and safe in the proposed concentrations.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packaging is common and suitable for the product.

The purpose was to develop capsules that would be bio-equivalent with innovator product Efexor XL marketed by Wyeth Laboratories/UK.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 upscaled batches of each strength in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification for the capsules includes tests for identity of drug substance, uniformity of mass, dissolution, assay, microbiological purity, net filled content, impurities and appearance. 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.

Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches of the 37.5 and 150 mg strengths in accordance with applicable European guidelines demonstrating the stability of the product over 36 months without any special storage conditions. On the basis of the data submitted, a shelf life was granted of 36 months, in PVC/Alu blister packaging or HDPE container without specific storage condition. The MAH committed to initiate also stability studies for the 75 mg capsules including dissolution studies.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of Efexor XL, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of 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.

The content of the SPC approved during the mutual recognition procedure is in line with the approved SPC of the innovator product Efexor XL 37.5, 75 and 150 mg prolonged release capsules.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Venfalex XR 75 mg is compared with the reference product Efexor XL 75 mg (Wyeth Laboratories, UK) under fed conditions. The use of the UK innovator product as reference product is justified, because of the essentially similar composition of the UK and NL originator products, and the comparable dissolution profiles of all available originator products. Although the Note for Guidance on the investigation of bioavailability and bioequivalence recommends using the highest dose, Venfalex XR 75 mg capsules were used mainly for ethical reasons. Previous experience with higher doses revealed a high incidence of nausea and vomiting in healthy volunteers. As the 37.5 and 150 mg capsules are dose-proportional, the production process is the same, the pharmacokinetics is linear over the dose range, and the dissolution profiles are comparable, extrapolation of the results obtained for the 75 mg prolonged release capsules to the 37.5 and 150 mg prolonged release capsules is considered acceptable.

A fasted study was not performed as the reference product has to be taken with food to improve tolerability. Moreover, according to the SPC of the reference product and literature, food is not expected to influence absorption of venlafaxine to a large degree. However, some member states only wanted to approve the application provided that bioequivalence was also shown in fasted condition. Therefore, the MAH committed to submit a bioequivalence study under fasted conditions as post-approval commitment.

Study 1 Single dose study
A randomised, single-dose, 2-way cross-over, bioavailability study was carried out under fed conditions in 30 healthy male subjects (including 6 standby subjects), aged 18-40 years. Subjects were not screened for CYP2D6 status (poor or fast metabolisers). Six subject were withdrawn from the trial because of medical grounds, protocol violation, vomiting and adverse events. A total of 24 subjects completed the study and were eligible for pharmacokinetic evaluation. Each subject had 2 dosing periods, separated by a washout period of 7 days. The bioavailability of the test Venfalex XR 75 mg capsule was compared to the reference product Efexor XL 75 mg capsule (Wyeth Laboratories, United Kingdom).

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

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	1471 ± 1589	1798 ± 1758	85 ± 37	6.0 (5.0-11.0)	10.1 ± 3.3
Reference	1330 ± 1319	1575 ± 1420	79 ± 31	6.5 (5.0–10.5)	9.6 ± 3.0
***Ratio (90% CI)**	1.07 (1.03-1.11)	1.10 (1.05-1.15)	1.06 (1.00-1.11)	--	--
CV (%)	7.1%	9.2%	10.3%	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
***** ln-transformed values

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

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	2824 ± 977	3091 ± 803	104 ± 38	10.5 (6.5–24.0)	15.4 ± 13.4
Reference	2642 ± 933	2964 ± 743	97 ± 31	10.5 (6.5–24.0)	17.9 ± 24.7‡
***Ratio (90% CI)**	1.07 (1.03-1.10)	1.04 (0.98-1.10)	1.05 (0.99-1.11)	--	--
CV (%)	6.3%	11.8%	10.6%	--	--

$AUC_{0-\infty}$ 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
‡ for one subject a value of 132 h was obtained

A high inter-subject variation was observed. Venlafaxine is a substrate for CYP2D6 and CYP3A4. In poor metabolisers the CYP2D6 pathway is impaired, resulting in high parent compound concentrations and low O-desmethyl-venlafaxine concentrations. Therefore, the high inter-subject variation can be probably explained by the inclusion of 3 poor metabolisers.

The 90% confidence intervals calculated for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. The t_{max} obtained for reference and test capsule were not statistically significantly different.

Study 2 Multiple dose study

A randomised, 2-treatment, multiple-dose, single-period, 2-sequence, cross-over, steady state bioavailability study was carried out under fed conditions in 32 healthy male subjects. Subjects were not screened for CYP2D6 status (poor or fast metabolisers). Two subjects were withdrawn from the study, because of adverse events. By protocol, the data of the first 24 subjects, who correctly completed the study, were used for pharmacokinetic and statistical analyses. One subject was replaced by the first replacement subject having the same sequence and completed the study. Each subject received daily a single dose of one of the 2 venlafaxine formulations. The capsule was administered with intake of food for 5 consecutive days. At day 6, subjects switched over to the other study medication, which was administered for 4 consecutive days.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of venlafaxine under fed conditions

Treatment	**AUC_τ** ng.h/ml	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	1821 ± 995	126 ± 56	39 ± 30	116 ± 38
Reference	1682 ± 913	118 ± 49	36 ± 28	105 ± 50
***Ratio (90% CI)**	1.09 (1.03-1.14)	1.06 (1.00-1.11)	1.12 (1.00-1.24)	1.16 (0.93-1.46)
CV (%)	9.0%	10.0%	21.3%	47.7%
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				

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of O-desmethyl-venlafaxine under fed conditions

Treatment	**AUC_τ** ng.h/ml	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	3139 ± 793	168 ± 38	92 ± 26	55 ± 16
Reference	2896 ± 759	155 ± 37	81 ± 27	58 ± 16
***Ratio (90% CI)**	1.09 (1.05-1.12)	1.08 (1.04-1.12)	1.15 (1.09-1.21)	0.95 (0.87-1.04)
CV (%)	5.7%	6.5%	10.7%	17.7%
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				

No washout period between the two treatment periods was present in the multiple dose study. This is acceptable since steady state is achieved in both periods (day 5 and day 9), and no carry-over effect is to be expected. The ANOVA analysis showed for venlafaxine and O-desmethyl-venlafaxine a treatment effect for AUC_τ and Cmax, while for venlafaxine AUC_τ also a period effect was observed. However, the statistical significant period and treatment effect is a result of the low variability observed in the studies.

The 90% confidence intervals calculated for AUCτ, C_{max} and C_{min} are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. The calculated PTF for venlafaxine and O-desmethyl-venlafaxine was not statistically significantly different. Based on the pharmacokinetic parameters of venlafaxine and O-desmethyl-venlafaxine under fed

conditions, it can be concluded that test Venfalex XR 75 mg capsule and reference Efexor XL 75 mg capsule are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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

The Venfalex XR 37.5, 75 and 150 mg prolonged release capsules are dose proportional. The pharmacokinetics of venlafaxine and O-desmethyl-venlafaxine are linear in the range 37.5-150 mg. The results of the bioequivalence study performed with the 75 mg capsule, therefore apply to the other capsule's 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 1994, 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 Risk Management Plan is not necessary for this product.

Readability Test

The package leaflet has been evaluated via an user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is consistent with that of the innovator reference product.

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

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Venfalex XR 37.5, 75 and 150 mg prolonged release capsules, with the reference product, and have therefore granted a marketing authorisation.

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

The PSUR submission cycle is 3 years. The 1st PSUR will cover the period from January 2007 until January 2010.

The date for the first renewal will be 18 January 2012.

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

Quality

Medicinal product

- The MAH committed to start additional stability studies for the 75 mg capsules.
- The MAH committed to start an in-use stability test for all three strengths.

Clinical

- The MAH committed to harmonise the SPC with the outcome of the article 30 referral to the CHMP for Efexor XL.
- The MAH committed that the finished product Venfalex XR prolonged release capsules, hard, will not be launched in some of the member states until a bioequivalence study under fasting conditions between the formulations from the test product and reference product has been accepted (see annex to the PAR).

List of abbreviations

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

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
Post-approval commitment; fasted bioequivalence study	NL/H/927/ 01-03/MR	post-approval commitment	NA	NA	Approved	Yes; 25 Jan 2008; Annex I

Annex I to the PAR

POST-approval commitment – Fasted bioequivalence study

During the mutual recognition procedure NL/H/927/01-03/MR the MAH committed to perform a bioequivalence study under fasted conditions between the formulations from the test product (Venfalex XR prolonged release capsules) and reference product (Efexor XL prolonged release capsules), because some member states only wanted to approve the application provided that bioequivalence was also shown in fasted condition.

For this post-approval commitment, the MAH has submitted one bioequivalence studies in which the pharmacokinetic profile of the test product Venfalex XR 75 mg is compared with the reference product Trevilor Retard 75 mg (Wyeth Pharma GmbH, Germany) under fasted conditions. The use of the DE innovator product as reference product is justified, because of the essentially similar composition of the DE and NL originator products, and the comparable dissolution profiles of all available originator products. Although the Note for Guidance on the investigation of bioavailability and bioequivalence recommends using the highest dose, Venfalex XR 75 mg capsules were used mainly for ethical reasons. Previous experience with higher doses revealed a high incidence of nausea and vomiting in healthy volunteers. As the 37.5 and 150 mg capsules are dose-proportional, the production process is the same, the pharmacokinetics is linear over the dose range, and the dissolution profiles are comparable, extrapolation of the results obtained for the 75 mg prolonged release capsules to the 37.5 and 150 mg prolonged release capsules is considered acceptable.

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).

Study 3 Bioequivalence study under fasted conditions
A randomised, single-dose, open label, bioequivalence study was carried out under fasting condition in 44 healthy adult male subjects. The data of the 35 subjects, who correctly completed the study, were used for pharmacokinetic and statistical analyses. Nine subjects were withdrawn from the study; 2 for positive drug-test, 6 for adverse events (5 vomiting and 1 case of fever, probably unrelated to drug), and 1 for lack of recovery in the second study phase. Each subject received daily a single dose of one of the 2 venlafaxine formulations. The capsule was administered with 240 mL of water. The wash-out period was 16 days.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of venlafaxine under fasted conditions

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	T_{max} h
Test	1171 ± 538	1201 ± 544	71.2 ± 27.2	6.29 ± 1.11
Reference	1188 ± 543	1217 ± 548	74.0 ± 26.1	6.34 ± 1.32
***Ratio (90% CI)**	0.99 (0.93-1.04)	0.99 (0.93-1.05)	0.95 (0.90-1.01)	--
CV (%)	14.3%	13.9%	14.3%	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
* ln-transformed values

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of O-desmethyl-venlafaxine under fasted conditions

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	T_{max} h
Test	3122 ± 1072	3164 ± 1072	108.4 ± 31.8	10.7 ± 2.36
Reference	3163 ± 962	3206 ± 970	114.3 ± 32.0	10.4 ± 2.44
***Ratio (90% CI)**	0.98 (0.93-1.03)	0.98 (0.93-1.03)	0.94 (0.90-1.00)	--
CV (%)	11.8%	11.7%	13.2%	--

$AUC_{0-\infty}$ 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
***** ln-transformed values

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of venlafaxine and O-desmethyl-venlafaxine under fasted conditions, it can be concluded that test Venfalex XR 75 mg capsule and reference Trevilor Retard 75 mg capsule are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Based on the review of the data of the bioequivalence study under fasted conditions, the concerned member states considered the post-approval commitment for Venfalex XR prolonged release capsules, hard, fulfilled. All concerned member states have therefore accepted the launch of the product in their national markets.