CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Venlafaxine Retard Mylan 37.5 mg, 75 mg, 150 mg, prolonged release capsules, hard Mylan B.V., the Netherlands

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/1091/01-03/DC
Registration number in the Netherlands: RVG 100004, 100007, 100014

19 October 2009

Pharmacotherapeutic group:	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; panic disorders, with or without agoraphobia.
Prescription status:	prescription only
Date of authorisation in NL:	25 September 2008
Concerned Member States:	Decentralised procedure with BE, DE, FR, HU, PL, PT, SK (all strengths), AT, CZ, DK, EL, ES, FI, IE, IT, NO, SE, SI and UK (only 75 mg and 150 mg)
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 Retard Mylan 37.5 mg, 75 mg and 150 mg, prolonged release capsules, hard, from Mylan B.V.. The date of authorisation was on 25 September 2008 in the Netherlands.

The product is indicated for:

- Major depressive episodes.
- Short-term treatment of generalised anxiety disorder.
- Short-term treatment of social anxiety disorder/ social phobia
- Treatment of panic disorders, 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 four bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Efexor XR 75 mg and 150 mg capsules from the Greek and Danish market. 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.

No paediatric development programme has been submitted.

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 very soluble in water. Venlafaxine hydrochloride contains a chiral centre but is manufactured as a racemate. There are two different polymorphic forms. Only one polymorphic was used and shown to be stable during storage.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacture
Venlafaxine hydrochloride is prepared via a two-step synthesis. Detailed information on the manufacture is included in the Restricted Part of the ASMF. The drug substance has been adequately characterized. The solvents used during the two reaction steps are adequately limited in the drug substance specifications. The MAH committed to submit an updated DMF when available.

Specification
The drug substance specification is in line with the Ph.Eur. with adequate additional specifications for polymorphic form, particle size, potential residual solvents, synthesis related impurities and microbiological quality.

Stability
Stability data have been obtained during storage at 25°C/60%RH (36 months) and 40°C/75%RH (6 months). The drug substance was packaged in a simulated commercial packaging. The solid drug substance can be regarded as stable and a re-test period of 36 months, when stored in the original package, was granted. The MAH committed to submit stability data of full scaled batches when available.

** 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 Retard Mylan 37.5 mg contains as active substance 42.43 mg of venlafaxine hydrochloride, corresponding to 37.5 mg of venlafaxine, and is an opaque, white prolonged release capsule, hard, marked with 'VEN' on one side of the capsule and '37.5' on the other side.

Venlafaxine Retard Mylan 75 mg contains as active substance 84.86 mg of venlafaxine hydrochloride, corresponding to 75 mg of venlafaxine, and is an opaque, flesh prolonged release capsule, hard, marked with 'VEN' on one side of the capsule and '75' on the other side.

Venlafaxine Retard Mylan 150 mg contains as active substance 169.71 mg of venlafaxine hydrochloride, corresponding to 150 mg of venlafaxine, and is an opaque, scarlet prolonged release capsule, hard, marked with 'VEN' on one side of the capsule and '150' on the other side.

The prolonged release capsules are packed in PVC/PE/PVDC/Aluminium foil blisters in cardboard packs of 7, 10, 14, 20, 25, 28, 30, 50, 56, 70, 90, 100, 500, 1000 capsules. The packaging chosen is the same as used for the innovator product.

The prolonged release capsules are packed in HDPE Bottles of 100 ml, 400 ml, 600 ml containing 7, 10, 14, 20, 25, 28, 30, 50, 56, 70, 90, 100 and 250 capsules.

The excipients are:
Contents of capsule
Hypromellose
Ammonio Methacrylate Copolymer (Type B)
Sodium Lauryl sulphate
Magnesium stearate

Coating
Ammonio Methacrylate Copolymer (Type B)

Capsule shell
Titanium dioxide E171
Gelatin
Red Iron Oxide E172 (75 mg only)
Erythrosine E127, Indigocarmine E132 (150 mg only)

Printing Ink
Shellac glaze
Iron oxide black

Pharmaceutical development
The MAH made the choice to manufacture prolonged release tablets that are subsequently packed into capsule shells. This leads to large capsules, but the choice for this drug product is adequately justified. The excipients used are common in the manufacture of prolonged release capsules. The packaging materials are usual and suitable for the product at issue. The three strengths are fully dose-proportional.

Manufacturing process
The drug product is prepared by means of wet granulation with organic (Class 3) solvents followed by tabletting and coating. Different tablet sizes are used for the various strengths. The tablets are encapsulated and packed into blisters.
The various steps of the manufacturing process, the process parameters, and the in-process controls have been sufficiently described. The manufacturing process is seen as a non standard process and process validation on three full scaled production batches is included.
The encapsulated tablets can be stored as intermediates in a double LDPE bag for six months. The MAH has submitted stability data for this intermediate in the proposed packaging used.

Product specification
The product specification includes tests for appearance, identity, uniformity of dosage units, the release rate of venlafaxine hydrochloride, loss on drying, residual solvents, related substances (degradation), assay of venlafaxine and microbiological quality.
Since an IVIVC is established the dissolution requirements are well-founded. The methods used for the assay and the related substances have been shown to be stability indicating. For all strengths batch analysis results of three production scaled batches have been provided. Compliance with the release requirements has been demonstrated.

Stability tests on the finished product
Three batches of each strength were stored at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH (up to 36 months long term). For none of the batches tested, a significant change is observed at both long term, intermediate and accelerated conditions. The water content increases during storage but remains well within the proposed end of shelf-life specifications. The values for the assay show fluctuating results where at certain timepoints values as low as 96% are observed. No trend is observed. The fluctuations are contributed to analytical variance. The values for the related substances remain not detected for the known impurities and very low for the unknown impurities at all timepoints and conditions. Results of a photostability study, performed according to the guideline, are included. The results show that the drug product is stable with respect to light. The MAH committed to submit stability data of full scaled batches when available.
On the basis of the currently available data a shelf-life of 36 months can be granted, without a special storage condition.

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 for gelatine and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. The magnesium stearate used is of 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.

Venlafaxine Retard Mylan 37.5 mg, 75 mg and 150 mg are modified release, multiple unit formulations. According to the guideline CPMP/EWP/280/96, three studies under fasting, fed and multiple dose (MD) conditions are required at the highest strength (*in casu* 150 mg). However, due to ethical reasons healthy volunteers could not be dosed with 150 mg under fasting and MD conditions. This demand was put forward by the MEB due to the established adverse effects, caused by the high dose of the drug substance. Only a fed study was allowed to be performed at the highest strength (150 mg), as venlafaxine is better tolerated when administered during or after a meal. To support the application, the MAH has submitted data of the 4 following bioequivalence studies in which the pharmacokinetic profile of the test product Venlafaxine Retard Mylan 75 mg and 150 mg is compared with the pharmacokinetic profile of the reference product, marketed in Greece (studies 1, 3 and 4) and Denmark (study 2):

1) A single dose study under fasted conditions with the 75 mg strength
2) A single dose study under fed conditions with the 75 mg strength
3) A multiple dose study under fed conditions with the 75 mg strength
4) A single dose study under fed conditions with the 150 mg strength

It was considered acceptable that the 150 mg multiple dose study was waived from the 75 mg capsule strength, as (a) the core of the mini-tablets are dose proportional, (b) the mini-tablets of different strengths are made by compression of granules of the same source, (c) the dissolution profile of the mini-tablets is

similar, and (d) venlafaxine display dose linear kinetics, (e) the different capsule formulations are manufactured by the same manufacturer.

The choice of the reference product
The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products in different member states.
The manufacturing process of the biobatches is identical to the manufacturing process intended for commercial production.

Design
All four studies were randomised, open-label, two-way cross-over studies. The wash-out period was 7 days for all studies. The capsules were taken with 240 ml of water.

Study 1: single dose, fasted conditions, 75 mg
Blood samples were taken at baseline and 1, 2, 3, 4, 5, 6, 6.33, 6.67, 7, 7.33, 7.67, 8, 8.5, 9, 10, 12, 16, 24, 36, 48, 72 and 96 hours post-dose.

Study 2: single dose, fed conditions, 75 mg
Blood samples were taken at baseline and 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72 and 96 hours post-dose.

Study 3: multiple dose, fed conditions, 75 mg
A single oral dose of venlafaxine as 1 x 75 mg extended-release capsule daily for 6 consecutive days was administered in each study period. Blood samples were collected prior to study drug administration on days 1, 4, 5, and 6 and at 1, 2, 3, 4, 5, 6, 6.33, 6.67, 7, 7.33, 7.67, 8, 8.5, 9, 10, 12, 16, and 24 hours post-dose on day 6, in each period.

Study 4: single dose, fed conditions, 150 mg
Blood samples were taken at baseline and 1, 2, 3, 4, 5, 6, 6.33, 6.67, 7, 7.33, 7.67, 8, 8.5, 9, 10, 12, 16, 24, 36, 48, 72 and 96 hours post-dose.

In the 150 mg single-dose fed study, the high-fat, high-caloric meal consisted of 800 to 1000 calories (approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat). The meal consisted of two eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 128 g of hash brown potatoes, and 200 mL of whole milk.
In the 75 mg single-dose fed study, the high-fat, high-caloric meal of two eggs fried in butter, 1 muffin with 11 g of butter, 2 strips of bacon, approximately 4 ounces of hash brown potatoes, and 240 mL of whole milk.

The study design and sampling times were considered acceptable by the member states. The fed studies were performed in line with the guideline. The analytical method is adequately validated and considered acceptable for analysis of the plasma samples.

Population
In all four studies, healthy adult subjects (males and females) were included. Mild smoking (< 10 cigarettes day) was not allowed in study 2. The subjects (mostly Caucasians) were not monitored for CYP2D6 status. However, a mixed population of poor and rapid metabolisers is in principle not a problem for bioequivalence studies, because of the cross-over design.

	Study 1 single dose, fasted, 75 mg	Study 2 single dose, fed, 75 mg	Study 3 Multiple dose, fed, 75 mg	Study 4 single dose, fed, 150 mg
Enrolled and randomized	28	44	36	28
Drop-out	3	1	0	2

Withdrawals	0	5 (3 vomiting, 2 food deviation#)	2 (1 AE allergic reaction, 1 vomiting)	3 (food deviation#)
PK analyses	24*	38	34	23

*According to the protocol, the first 24 subjects were included in PK analyses, # less than 40% of the high fat meal was consumed

Statistical methods

ANOVA analyses were performed on ln transformed PK parameters. Covariates in the ANOVA model were sequence, subject within sequence, period and treatment.

Primary criterion for bioequivalence was when 90% CI of the test/reference ratio for $AUC_{0-\tau}$ and $C_{max,ss}$ should be within 0.80-1.25 for multiple dose studies, and the same for C_{max} and AUC_{0-t} in the single dose studies. Statistical analyses were performed for the active substance. The statistical analysis of the parameters of the metabolite were considered as supportive. The statistical analyses were performed using SAS®. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Study 1 - single dose, fasted, 75 mg

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	641.1 ± 518.0	697.7 ± 542.8	35.8 ± 14.5	6.33 (5-36)	-
Reference	623.7 ± 390.4	675.4 ± 411.4	34.6 ± 15.2	6.67 (5-9)	-
***Ratio (90% CI)**	1.00 (0.87-1.15)	0.99 (0.86-1.15)	1.05 (0.97-1.14)	-	-
CV (%)	29.3	28.6	16.0	-	-

$AUC_{0-\infty}$ 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*

Study 2 - single dose, fed, 75 mg

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

Treatment N=38	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	986.7 ± 635.5	1055.6 ± 631.8	65.5 ± 26.3	6.25 (3-12)	-
Reference	1042.2 ± 790.0	1108.3 ± 802.2	69.6 ± 26.3	5.5 (4-10)	-
***Ratio (90% CI)**	0.92 (0.87-0.94)	0.99 (0.94-1.06)	0.92 (0.87-0.98)	-	-
CV (%)	14.9	15.6	15.4	-	-

$AUC_{0-\infty}$ 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*

Study 3 - multiple dose, fed, 75 mg

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

Treatment N=34	**$AUC_{0-\tau}$** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF%** %
Test	893.5 ± 682.3	59.4 ± 36.5	20.0 ± 20.9	127.2 ± 47.4
Reference	820.2 ± 593.6	57.4 ± 32.4	18.5 ± 18.2	132.4 ± 35.4
***Ratio (90% CI)**	1.06 (0.99-1.14)	1.09 (0.95-1.07)	0.95 (0.80-1.12)	
CV (%)	17.5	14	42	
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				

Study 4 – single dose, fed, 150 mg

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

Treatment N=23	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1849.9 ± 774.3	1912.9 ± 794.0	120.1 ± 58.6	8 (5-10)	-
Reference	1895.5 ± 899.5	1932.9 ± 902.0	114.7 ± 48.3	5 (4-9)	-
***Ratio (90% CI)**	0.99 (0.95-1.04)	1.00 (0.96-1.04)	1.03 (0.98-1.07)		-
CV (%)	8.9	8.0	8.9		-
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Conclusion – 75 mg strength

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 in studies 1

(fasted conditions) and 2 (fed conditions). Further, the 90% confidence intervals calculated for $AUC_{0-\tau}$ and C_{max} in the multiple dose study 3 (fed conditions) are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of venlafaxine under fasted and fed conditions, it can be concluded that Venlafaxine Retard Mylan 75 mg and the reference capsule are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Conclusion 150 mg strength
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 in study 4. Based on the pharmacokinetic parameters of venlafaxine under fed conditions, it can be concluded that Venlafaxine Retard Mylan 150 mg and the Greek reference capsule are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Discussion food effect
According to the literature and SPC of the reference product, food has no effect on the absorption of venlafaxine. However, the mean PK parameters were approximately 50% higher in the fed study compared to the fasted study. Direct comparisons between the fed and fasted study could not be made as the studies were performed with different subjects, in different CRO sites and using different bioanalytical methods. Considering the relatively large inter-individual variability of venlafaxine (partly due to the large first-pass effect mediated by CYP2D6 and the relatively high incidence of poor CYP2D6 metabolisers in Caucasians) a difference of 50% between two populations is not surprising. Therefore, the MEB concluded that it seems not likely that the observed difference would be related to food status alone.

However, during the procedure a potential serious risk to public health was raised by one of the member states regarding the outcome of the single-dose fasting and single-dose fed studies. The data suggested strongly a dose-dumping effect by food, whereas this food-effect is not known for the reference product. Considering the above mentioned food effect, a single-dose study under fasting conditions was requested.

The MAH gave a satisfactorily written reply to this concern. All member states agreed that although in the fed studies plasma levels of venlafaxine were approximately 50% higher compared to the studies in fasted conditions, this does not indicate that this is due to dose dumping of the test product, as the plasma values of the reference product were enhanced to the same extent in the fed study compared to the fasted study. Bioequivalence was thus confirmed in both the fed and fasted condition.
From the reference product it is known that food has no influence on bioavailability, and it may be concluded that the relatively high exposure of the reference product in the fed study is rather due to other factors than food. Venlafaxine is mainly metabolised by CYP2D6, and both poor and fast metabolisers were included at-random in the studies. Considering the known large inter-individual variability of venlafaxine, a difference of 50% between two populations is not at all a surprising finding.

Extrapolation of results to other strengths
The results of the studies with the 75 mg formulation can be extrapolated to the 37.5 mg capsule, according to conditions in Note for Guidance 280/96. The only (slight) difference between the 37.5 and 75 mg tablets is a very small difference in the amount of tablet coating, which has no release controlling properties. Furthermore, kinetics of venlafaxine are linear and the dissolution profiles of 37.5, 75 mg and 150 mg test-reference capsules are similar at pH 1.2/4.5/6.8. A separate study was performed for the 150 mg capsule. In principle, the conclusions of the 75 mg studies could be extrapolated to the 150 mg capsule strength as well.

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. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC and PIL have been harmonised with the final Product Information for procedures NL/H/927/01-03 through NL/941/01-03, which concern Venlafaxine registrations. Furthermore the MAH has committed to harmonise the SPC and PIL with that of the innovator upon finalisation of the article 30 referral.

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. After a pre-round with 2 participants, two cohorts of 10 participants were interviewed. After the first round of 10 participants, the section *If you stop taking Venlafaxin* in the PIL was amended.
Diagnostic testing was performed. Questions were asked about all parts of the leaflet (18 in total: 6 general questions and 12 specific questions).
The results show that the package leaflet meets the criteria for readability as set in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Venlafaxine Retard Mylan 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 at the highest strength (*in casu* 150 mg). However, due to ethical reasons healthy volunteers could not be dosed with 150 mg under fasting and multiple dose conditions. It was considered acceptable by all member states that the four following bioequivalence studies were performed: 1) a single dose study under fasted conditions with the 75 mg strength; 2) a single dose study under fed conditions with the 75 mg strength; 3) a multiple dose study under fed conditions with the 75 mg strength and 4) a single dose study under fed conditions with the 150 mg strength. Bioequivalence was shown for the 75 mg and 150 mg strength with the reference product. The results of the studies with the 75 mg strength could be extrapolated to the 37.5 mg strength.

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

The SPC is consistent with that of the SPC of another venlafaxine generic product (NL/H/927-941/01-03). The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Venlafaxine Retard Mylan 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 21 May 2008. Venlafaxine Retard Mylan 37.5 mg, 75 mg and 150 mg capsules were authorised in the Netherlands on 25 September 2008.

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

The date for the first renewal will be: 21 May 2013.

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

<u>Quality - active substance</u>
- The MAH committed to submit an updated DMF when available.
- The MAH committed to submit stability data of full scaled batches when available.

<u>Quality - medicinal product</u>
- The MAH committed to submit stability data of full scaled batches when available.

<u>Product information</u>
- The MAH committed to harmonise the product information with the outcome of the article 30 referral for the innovator product.

List of abbreviations

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

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Addition of a manufacturing site of the finished product for the 75 mg strenght only	NL/H/1091/002 /IB/001	IB	3-9-2008	3-10-2008	Approval	N
Minor change in the manufacture of the finished product	NL/H/1091/002 /IB/002	IB	3-9-2008	3-10-2008	Approval	N
Change in analytical method to determine impurities in the drug substance and consequentially a change in analytical method to determine impurities in the drug product.	NL/H/1091/001 -003/IB/003	IB	3-9-2008	3-10-2008	Approval	N
Addition of an alternative active pharmaceutical ingredient (API) supplier.	NL/H/1091/001 -003/IA/004	IA	3-9-2008	17-9-2008	Approval	N
Addition of an alternative active pharmaceutical ingredient (API) supplier.	NL/H/1091/001 -003/IA/005	IA	3-9-2008	17-9-2008	Approval	N
To register a change in the address of the Marketing Authorisation Holder.	NL/H/1091/001 -003/IA/006	IA	16-10-2008	30-10-2008	Approval	N
Change of product name in Spain	NL/H/1091/003 /IB/007	IB	16-10-2008	15-11-2008	Approval	N
Addition of pack type	NL/H/1091/001 -003/II/009	II	11-2-2009	23-9-2009	Approval	N
Addition of API manufacturer	NL/H/1091/001 -003/II/010	II	2-3-2009	7-8-2009	Approval	N
Update of SPC, package leaflet and labelling	NL/H/1091/001 -003/II/011	II	3-6-2009	--	Suspended	N
Submission of a new or udated Ph.Eur. Certificate of Suitability for an active substance manufacturer currently approved.	NL/H/1091/001 -003/IA/013	IA	17-8-2009	31-8-2009	Approval	N
Addition of a manufacturing and batch control site.	NL/H/1091/001 -003/IB/014	IB	07-09-2009	7-10-2009	Approval	N
Addition of a batch release and batch control/testing site.	NL/H/1091/001 -003/IA/015	IA	7-9-2009	21-9-2009	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/1091/001 -003/IA/017	IA	28-9-2009	12-10-2009	Approval	N