Public Assessment Report

Venlafaxine 37.5mg Tablets
PL 14017/0120

Venlafaxine 75mg Tablets
PL 14017/0121

Marketing Authorisations Cancelled
VENLADEX 37.5MG AND 75MG TABLETS

PL 14017/0124-5

(venlafaxine hydrochloride)

Dexcel Pharma Limited

LAY SUMMARY

The MHRA granted Dexcel Pharma Limited Marketing Authorisations (licences) for the medicinal products ViePax 37.5mg and 75mg tablets (PL 14017/0120-1) and VENLADEX 37.5mg and 75mg tablets (PL 14017/0124-5). These are prescription only medicines (POM) used in the treatment of major depressive episodes and for the prevention of recurrence of major depressive episodes.

ViePax and VENLADEX are antidepressants that belong to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). It is thought that people who are depressed have lower levels of serotonin and noradrenaline in the brain. It is not fully understood how antidepressants work, but they may help by increasing the levels of serotonin and noradrenaline in the brain.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefit of taking these products outweighs the risks, hence Marketing Authorisations have been granted.

Changes following approval of the initial Authorisations:

On 26 December 2013 the Marketing Authorisations for Venladex 37.5mg and 75mg Tablets (PL 14017/0124-5) were cancelled at the request of the MA holder.

On 3 January 2017 a variation was granted to change the product names from ViePax 37.5mg tablets to Venlafaxine 37.5mg tablets

ViePax 37.5MG AND 75MG TABLETS

PL 14017/0120-1

Marketing Authorisations Cancelled

VENLADEX 37.5MG AND 75MG TABLETS

PL 14017/0124-5

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the MHRA granted marketing authorisations for the medicinal products ViePax 37.5mg and 75mg tablets (PL 14017/0120-1) and VENLADEX 37.5mg and 75mg tablets (PL 14017/0124-5) to Dexcel Pharma Limited on 25th November 2008. The products are prescription only medicines (POM) used in the treatment of major depression episodes and for the prevention of recurrence of major depressive episodes.

These applications have been made under the first paragraph of Article 10.1(a) (iii) of Directive 2001/83/EC, as amended, claiming essential similarity to the reference medicinal products in the UK, Efexor 37.5mg and 75mg Tablets (PL 00011/0199 & 0201) authorised to Wyeth Laboratories in November 1994.

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-desmethylvenlafaxine (ODV), are inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Venlafaxine and its active metabolite reduce β-adrenergic responsiveness after both acute (single dose) and chronic administration. Venlafaxine and ODV are very similar with respect to their overall action on neurotransmitter reuptake and receptor binding.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

INN: Venlafaxine hydrochloride

Chemical names:
(a) (±)-1-[2-(Dimethylamino)-1-(4-methoxy phenyl)ethyl]cyclohexanol hydrochloride
(b) (N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyleneamine hydrochloride

Structure

Molecular formula: $C_{17}H_{27}NO_2$.HCl.

Molecular Mass: 313.91

General Properties

Venlafaxine hydrochloride is a white to almost white powder that is freely soluble in water and freely soluble in methanol, soluble in anhydrous ethanol and practically insoluble in acetone.

This is subject to a Drug Master File (DMF). A valid letter of access has been provided.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Satisfactory characterisation of the drug substance has been provided in the Drug Master File from the Drug Substance Manufacturer (DSM) and by the Finished Product Manufacturer (FPM).

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active venlafaxine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Stability data have been provided in accordance with regulatory requirements and support the declared retest interval.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, lactose monohydrate, povidone, magnesium stearate, ferric oxide yellow E172, ferric oxide brown E172, Ethanol 96% and sodium starch glycolate.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of ferric oxide yellow and brown which are controlled to EC Guideline specifications. Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

Lactose monohydrate is the only ingredient that comes from an animal source. The lactose used to produce lactose monohydrate is sourced from healthy animals under the same conditions as milk collected for human consumption.

The magnesium stearate used is stated as being of plant origin.

Dissolution

Dissolution and impurity profiles for all strengths of the drug product were found to be equivalent to those of the reference products.

Manufacturer(s)

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure system

The product is packaged in Aclar coated PVC/aluminium blister. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 3 years with no storage condition has been set and this is satisfactory.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The proposed products are considered to be a generic medicinal product to the reference products with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

These are National Abridged applications for immediate-release tablets containing 37.5 mg and 75 mg of the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine, claiming essential similarity to the UK brand leader Efexor, PL 00011/0199, 0201 (37.5 mg & 75 mg tablets respectively) which has been licensed in the UK for more than 10 years (Nov. 1994) to Wyeth Laboratories.

2. BACKGROUND

Venlafaxine is well characterised in the literature. It is a structurally novel antidepressant that is chemically unrelated to tricyclic, tetracyclic or other available antidepressants. It is a racemate with 2 enantiomers.

3. INDICATIONS

Treatment of major depressive episodes.

For prevention of recurrence of major depressive episodes.

4. DOSE & DOSE SCHEDULE

This is consistent with the reference product.

5. TOXICOLOGY

No new data are submitted and the pre-clinical expert report identifies no new concerns.

6. CLINICAL PHARMACOLOGY

6.1 PHARMACODYNAMICS

No new data submitted. The pharmacodynamics of venlafaxine are well described. The mechanism of its 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 ODV are potent neuronal serotonin and noradrenaline re-uptake inhibitors (SNRI) and weak inhibitors of dopamine re-uptake. In addition, venlafaxine and ODV reduce β-adrenergic responsiveness in animals after both acute (single dose) and chronic administration. Venlafaxine and its major metabolite appear to be equipotent with respect to their overall action on neurotransmitter re-uptake.

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.

6.2 PHARMACOKINETICS

No new data submitted. The pharmacokinetics of venlafaxine are well described. It is well absorbed (>92%) and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/ml after 25 to 150mg single doses, and are reached in approximately 2.4 hours. Venlafaxine

is extensively metabolised in the liver. O-desmethylvenlafaxine is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Mean peak O-desmethyl venlafaxine plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Venlafaxine and O-desmethylvenlafaxine are 27% and 30% bound to plasma proteins respectively. O-desmethylvenlafaxine, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

6.3 BIOEQUIVALENCE

A single bioequivalence study is presented for the 75mg strength, carried out in compliance with Good Clinical Practice.

As the present applications for both strengths are supported by a single biostudy on the higher 75mg strength, it is necessary to consider the linearity of kinetics over the therapeutic range i.e. up to the maximum recommended dose of 375mg per day. Venlafaxine is virtually completely absorbed at therapeutic doses from either tablet or oral solution. The Clinical expert report quotes a reference showing kinetics to be linear up to 450mg. This is satisfactory. As kinetics are linear, a further study is not required for the 37.5mg preparation if the excipients are qualitatively and quantitatively the same in both and dissolution behaviour is similar.

As the Efexor SPC advises that "it is recommended that Efexor be taken with food" the biostudy was done under fed conditions. Dosing was 30 minutes after the start of a standardised breakfast (27g fat, 29g protein, 73g carbohydrate, 650Kcal). This is appropriate. Bioavailability is unaffected by food.

Study BES/026/02

In this comparative, randomised, two-way, two-period, single dose crossover study, 30 healthy fed male volunteers received 75mg orally of either the applicant's test product or the reference product Efexor 75mg Tablet (John Wyeth & Brother Ltd, UK). Serum drug levels were followed for 60 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The washout period between phases was sufficiently long at 2 weeks.
The randomisation scheme was balanced for sequence and appears random.
Data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA, both log-transformed and non-transformed. T_{max} was analysed non-parametrically.

Results
Four subjects were withdrawn from the study due to vomiting following dosing (3 in period 1, 1 in period 2). These subjects were excluded from the study. There were no other major protocol deviations or sequence or period effects. The treatment of these subjects and their exclusion from the analysis was according to protocol and satisfactory. The conclusions of the study are not considered to be affected.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals for both the parent compound and the active metabolite:

Pharmacokinetic results (mean ± SD and (range)) for a randomised single dose 2-way crossover study between the test and reference products.

Test parameter	Test product	Reference product	Ratio Test/reference x 100	90% Confidence intervals
Venlafaxine				
AUC_{0-t} (ng.h/ml)	718.51 ± 765.30 (192.72-3145.65)	760.47 ± 768.79 (215.65-3181.24)	0.92	0.83-1.01
$AUC_{0-\infty}$ (ng.h/ml)	770.37 ± 807.12 (227.89-3381.40)	811.49 ± 810.14 (244.04-3369.23)	0.93	0.85-1.02
C_{max} (ng/ml)	86.41 ± 40.14 (29.46-189.34)	92.36 ± 41.53 (33.72-214.08)	0.93	0.87-1.00
T_{max} (h)	2.67 ± 1.03 (1.00-4.50)	2.37 ± 1.05 (1.00-5.00)	-	-
$T_{½}$	5.02 ± 3.11 (2.53-15.80)	4.98 ± 2.97 (2.50-14.80)	-	-
O-desmethylvenlafaxine				
AUC_{0-t} (ng.h/ml)	2488.23 ± 808.56 (746.50-3991.19)	2534.14 ± 723.66 (643.96-3803.00)	0.97	0.90-1.04
$AUC_{0-\infty}$ (ng.h/ml)	2567.12 ± 804.60 (853.20-4103.15)	2608.62 ± 716.75 (783.00-3885.60)	0.97	0.91-1.04
C_{max} (ng/ml)	136.48 ± 53.57 (20.78-213.50)	138.56 ± 47.12 (16.51-209.55)	0.97	0.89-1.04
T_{max} (h)	4.56 ± 2.33 (2.00-12.00)	4.79 ± 2.18 (1.50-12.00)	-	-
$T_{½}$	11.53 ± 3.59 (6.58-24.08)	11.14 ± 3.09 (7.79-20.95)	-	-

Assessor's Comment

Bioequivalence has been satisfactorily demonstrated in accordance with CPMP criteria for both the parent compound and the active metabolite. A further bioequivalence study is not required for the 37.5mg tablet strength, as linear kinetics apply over the proposed dose range and the Pharmaceutical Assessor has confirmed that the two strengths are based on a proportional formulation and similar dissolution profiles occur for the two strengths.

7. EFFICACY

No new data submitted.

8. SAFETY

No new data submitted.

9. EXPERT REPORTS

Satisfactory expert reports for each strength are provided by an appropriately qualified pharmaceutical physician.

10. PATIENT INFORMATION LEAFLET (PIL)

These are satisfactory.

11. LABELLING

These are satisfactory.

12. APPLICATION FORM (MAA)

The MAAs are medically satisfactory.

13. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are satisfactory.

14. DISCUSSION

The requested indications and other product literature details are satisfactory and Bioequivalence to the reference product has been shown.

15. MEDICAL CONCLUSION

Marketing Authorisations should be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of ViePax 37.5mg and 75mg tablets and VENLADEX 37.5mg and 75mg tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

A bioequivalence study was carried out and the test and reference products shown to be bioequivalent for the appropriate pharmacokinetic criteria.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and Labels are satisfactory and consistent with that for the UK reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with ViePax and VENLADEX 37.5mg and 75mg tablets is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

ViePax 37.5MG AND 75MG TABLETS

PL 14017/0120-1

VENLADEX 37.5MG AND 75MG TABLETS

PL 14017/0124-5

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 29 June 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 14th July 2004
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 11th May 2005, 29th June 2006 and 5th June 2007
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 26th December 2005, 20th April 2007, and 5th October 2007
5	The applications were determined on 25th November 2008

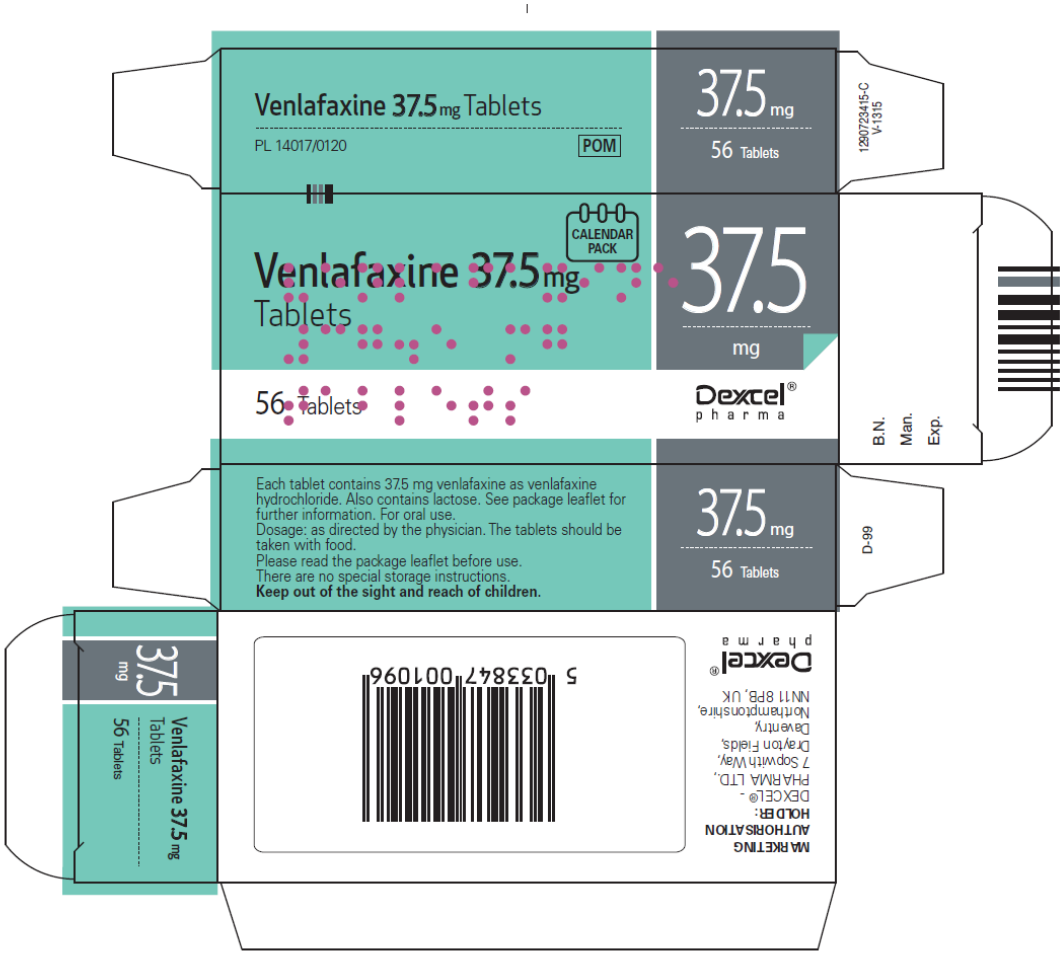
SUMMARY OF PRODUCT CHARACTERISTICS

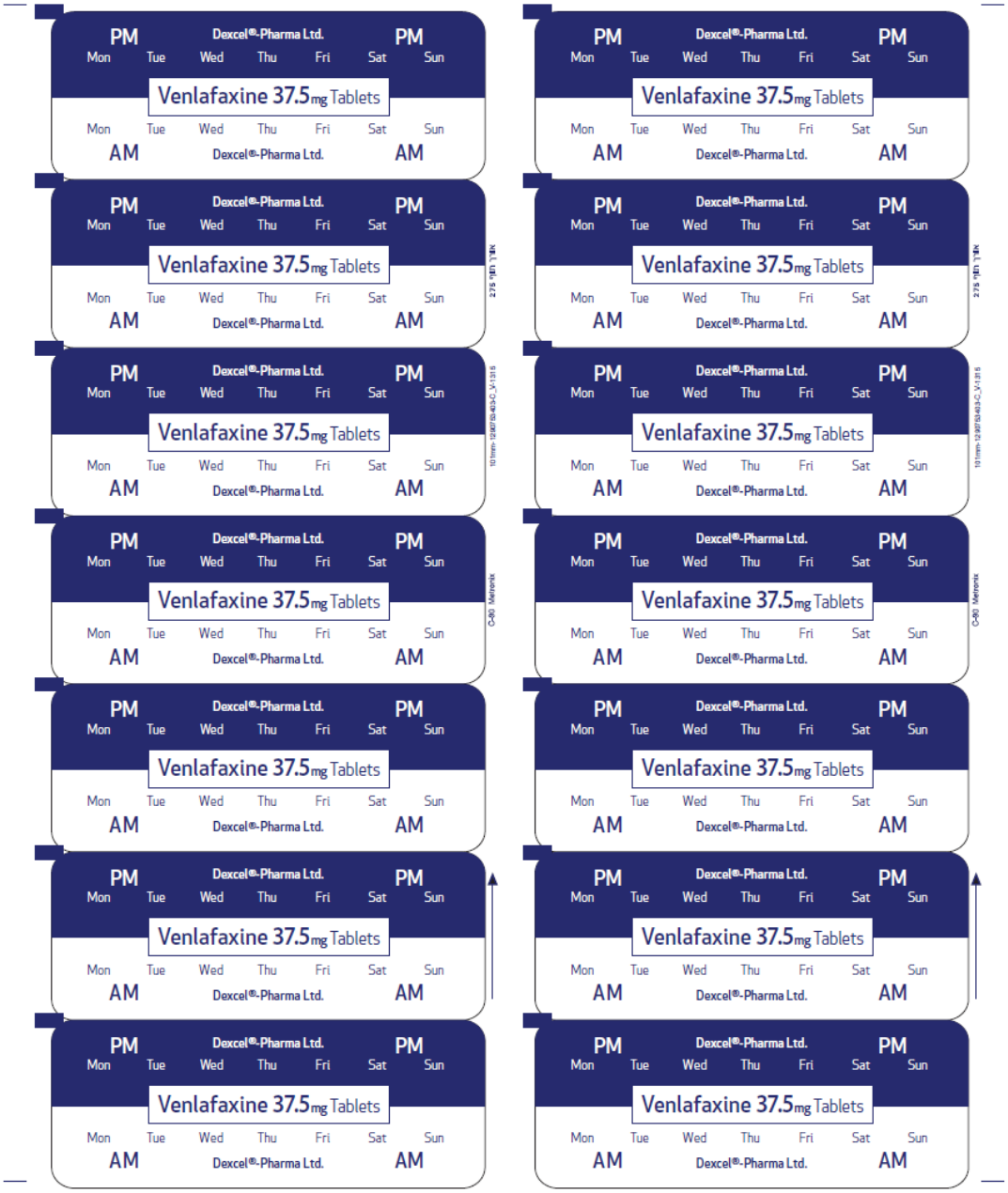
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING


Venlafaxine 37.5 mg Tablets
PL 14017/0120
POM
37.5 mg
56 Tablets
1290723415-C
V-1315
CALENDAR PACK
Venlafaxine 37.5 mg
Tablets
37.5
mg
56 Tablets
Dexcel pharma
B.N.
Man.
Exp.
Each tablet contains 37.5 mg venlafaxine as venlafaxine hydrochloride. Also contains lactose. See package leaflet for further information. For oral use.
Dosage: as directed by the physician. The tablets should be taken with food.
Please read the package leaflet before use.
There are no special storage instructions.
Keep out of the sight and reach of children.
37.5 mg
56 Tablets
D-99
5 033847 001096
MARKETING AUTHORISATION HOLDER:
DEXCEL® - PHARMA LTD.,
7 Sopwith Way,
Drayton Fields,
Daventry,
Northamptonshire,
NN11 8PB, UK
Dexcel pharma
37.5 mg
Venlafaxine 37.5 mg
Tablets
56 Tablets


PM
Dexcel®-Pharma Ltd.
PM
Mon Tue Wed Thu Fri Sat Sun
Venlafaxine 37.5mg Tablets
Mon Tue Wed Thu Fri Sat Sun
AM
Dexcel®-Pharma Ltd.
AM


Venlafaxine 75mg Tablets
PL 14017/0121
75 mg
56 Tablets
1230/72446-C
V-1315
CALENDAR PACK
Venlafaxine 75mg
Tablets
75
mg
56 Tablets
Dexcel pharma
B.N.:
Man:
Exp.:
MARKETING AUTHORISATION HOLDER:
DEXCEL® - PHARMA LTD.,
7 Sopwith Way, Drayton Fields, Daventry,
Northamptonshire, NN11 8PB, UK
POM
75 mg
56 Tablets
D-204
Venlafaxine 75mg Tablets
Each tablet contains 75 mg venlafaxine as venlafaxine hydrochloride. Also contains lactose. See package leaflet for further information. For oral use.
Dosage: as directed by the physician. The tablets should be taken with food.
Please read the package leaflet before use.
There are no special storage instructions.
Keep out of the sight and reach of children.
5 033847 001102


Dexcel®-Pharma Ltd.
Mon Tue Wed Thu Fri
Sat Sun PM
Venlafaxine 75mg Tablets
Mon Tue AM
Wed Thu Fri Sat Sun
Dexcel®-Pharma Ltd.

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)
Cancellation of Market Authorisations for PL 14017/0124 and PL 14017/0125	N/A	N/A	N/A	26/12/2013 (date of cancellation)	Approved	N
To make editorial amendments to SmPC sections 4.4, 4.5, (4.6 in PL 14017/0122) 4-9. To update sections 5.1 in line with the reference product Efexor	N/A	SmPC	29/05/2018	28/06/2018	Approved	Yes Annex 1
To change the product name from ViePax 37.5mg tablets to Venlafaxine 37.5mg tablets.	N/A	N/A	2/12/2016	03/01/2017	Approved	N

ANNEX 1

Our Reference: PL 14017/0120 - 0042
PL 14017/0121 - 0041

Product: Venlafaxine 37.5mg Tablets
Venlafaxine 75mg Tablets

Marketing Authorisation Holder: Dexcel Pharma limited
Active Ingredient(s): Venlafaxine hydrochloride.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable):

Reason:
To update SmPC sections 4.4, 4.5, (4.6 in PL 14017/0122) 4.9 and 5.1 in line with the reference product Efexor.

Supporting Evidence
Revised SmPC fragments and PILs and SmPCs and PILs for the brand leader (Efexor XL 75 mg and 150 mg)

Evaluation
Only the SmPC was updated within this variation as follows, sections 4.4, 4.5 and 4.9 with editorial/typographical changes only. Section 5.1 was updated for all strengths in line with the brand leader Efexor. Section 4.6 was additionally updated for PL 14017/0122 only.

There was no change to the reference product PIL and the changes to the SPC do not reflect the PIL. Therefore, PIL mockups were not submitted.

This variation included additional Marketing Authorisations: PL 14017/0120 and PL 14017/0121.

Conclusion
The proposed changes to the SmPCs and PILs are acceptable.

Decision - Approved on 28 June 2018.