ViePax XL 75 MG AND 150 MG PROLONGED-RELEASE TABLETS

PL 14017/0118-9

VENLADEX XL 75 MG AND 150 MG PROLONGED-RELEASE TABLETS

PL 14017/0122-3

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LAY SUMMARY

ViePax XL 75 mg and 150 mg prolonged-release tablets
Venladex XL 75 mg and 150 mg prolonged-release tablets
(venlafaxine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for ViePax XL 75 mg and 150 mg prolonged-release tablets (PL 14017/0118-9) and Venladex XL 75 mg and 150 mg prolonged-release tablets (PL 14017/0122-3). It explains how ViePax XL 75 mg and 150 mg prolonged-release tablets (PL 14017/0118-9) and Venladex XL 75 mg and 150 mg prolonged-release tablets (PL 14017/0122-3) were assessed and the authorisations recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets.

For practical information about using ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets and what are they used for?
ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets are 'generic' medicines. This means that ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets are similar to a reference medicine already authorised in the European Union (EU) called Efexor XL 75 mg and 150 mg Capsules (Wyeth Laboratories, UK).

ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets contain the active ingredient, venlafaxine (as venlafaxine hydrochloride). ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets are used to treat depression, severe and persistent anxiety known as generalised anxiety disorder (GAD), social anxiety disorder (also known as social phobia) and panic disorder (panic attacks).

How do ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets work?
ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets contain the active ingredient, venlafaxine (as venlafaxine hydrochloride). Venlafaxine is an antidepressant that belongs to a group of medicines called serotonin and norepinephrine reuptake inhibitors (SNRIs). This group of medicines is used to treat depression and other conditions such as anxiety disorders. It is thought that people who are depressed and/or anxious 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.

How are ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets used?
ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets can be obtained only with a prescription. This medicine should be taken exactly as advised by the prescribing doctor. The dose advised for treatment and its duration will depend on the reason why this medicine has been prescribed.

ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets are taken by mouth at approximately the same time each day, either in the morning or in the evening. The tablets must be swallowed whole with fluid and not crushed, divided, chewed or dissolved. ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets should be taken with food.

For further information on how ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets are used, please see the Summary of Product Characteristics available on the MHRA website.

What benefits of ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets have been shown in studies?
As ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets are generic medicines, studies in patients have been limited to tests to determine that the tablets are similar to the reference medicine, Efexor XL 75 mg and 150 mg Tablets (John Wyeth & Brother Ltd, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets?
Because ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets are generic medicines and are bioequivalent to the reference medicine, the benefits and possible effects are taken as being the same as those for the reference medicine.

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why are ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets approved?
It was concluded that, in accordance with EU requirements, ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets have been shown to have comparable quality and to be bioequivalent to Efexor XL 75 mg and 150 mg Tablets (John Wyeth & Brother Ltd, UK). Therefore, the MHRA decided that, as for Efexor XL 75 mg and 150 mg Tablets (John Wyeth & Brother Ltd, UK) the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets.

Marketing Authorisations were first granted in the UK on 19 November 2008.

The full PAR for ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets follows this summary.

For more information about treatment with ViePax/Venladex XL 75 mg and 150 mg prolonged-release tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2014.

Viepax XL 75 MG AND 150 MG PROLONGED-RELEASE TABLETS

PL 14017/0118-9

VENLADEX XL 75 MG AND 150 MG PROLONGED-RELEASE TABLETS

PL 14017/0122-3

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 XL 75 mg and 150 mg prolonged-release tablets (PL 14017/0118-9) and VENLADEX XL 75 mg and 150 mg prolonged-release tablets (PL 14017/0122-3) to Dexcel Pharma Limited on 19th November 2008. These products are prescription only medicines (POM).

These applications have been made under the last paragraph of Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to the brand leader products in the UK, Efexor XL 75 mg and 150 mg Capsules (PL 00011/0223 & 0224) authorised to Wyeth Laboratories in August 1997. These formulations are capsules containing coated spheroids.

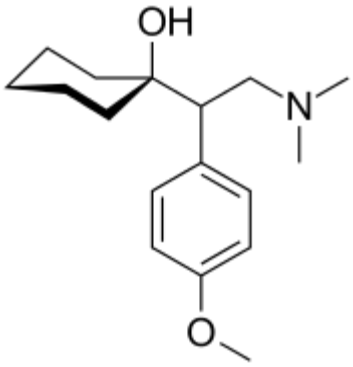
The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the central nervous system. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are inhibitors of serotonin 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: 313.9

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, Hypromellose 2208, ethylcellulose, magnesium stearate, silica, colloidal anhydrous, ethanol 96%, ethylcellulose aqueous dispersion, dibutyl sebacate, hypromellose, macrogol 400, and water purified. ViePax/VENLADEX XL 150 mg tablets also contain carnauba wax.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of ethylcellulose aqueous dispersion and dibutyl sebacate that are controlled to USP/NF specifications. Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

The current TSE certificate for Magnesium Stearate has been provided.

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. The 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.

SmPC, PIL, Labels
The SmPCs, PILs 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.

NON-CLINICAL ASSESSMENT

No new NON-clinical 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 once daily prolonged-release tablets containing 75mg and 150mg of the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine. These applications have been made under the last paragraph of Article 10.1 of Directive 2001/83/EC, as amended, cross-referring to the original product Effexor, authorised to Wyeth Laboratories in France in May 1994. The applications represent a change in pharmaceutical form and pharmacokinetics from the immediate-release product (both strengths) and a change in strength for the 150mg tablet. The reference medicinal products in the UK are Efexor XL 75mg and 150mg Capsules (PL 00011/0223 & 0224) authorised to Wyeth Laboratories in August 1997. This legal basis is satisfactory.

Venlafaxine is one of a number of SSRIs and related substances involved in an ongoing CHMP referral relating to safety and efficacy in children. There is no paediatric development plan for these generic products.

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.
- Treatment of social anxiety disorder.

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-lifes of venlafaxine and O-desmethylvenlafaxine are 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

Two bioequivalence studies for each strength, one fasted and one fed in each case, are presented in support of these applications. All were carried out in compliance with Good Clinical Practice.

Bioequivalence of 75 mg products

Study BES/020/02 – Fasted, 75 mg strength

In this comparative, randomised, two-way, two-period, single dose crossover study, 38 healthy fasted male volunteers received 75 mg orally of either the applicant's test product or the reference product Efexor XL 75 mg 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 1 week.

Results

Two subjects were withdrawn due to vasovagal syncope and gastroenteritis. Their data were excluded from the analysis, which is satisfactory. Bioequivalence results (mean + SD and (range)) for log-transformed test/reference ratios (ANOVA) with 90% Confidence Intervals for parent compound and active metabolite:

Test parameter	Test product	Reference product	Ratio Test/reference (geometric means)	90% ANOVA Confidence intervals
Venlafaxine				
AUC_{0-t} (ng.h/ml)	623.52 ± 439.44 (73.57-2031.79)	568.50 ± 370.48 (143.71-1785.91)	1.05	0.94-1.18
$AUC_{0-\infty}$ (ng.h/ml)	666.93 ± 437.79 (80.64-2088.22)	623.25 ± 373.77 (170.83-1868.75)	1.02	0.90-1.14
C_{max} (ng/ml)	37.96 ± 19.90 (11.11-88.42)	37.46 ± 17.42 (9.96-75.19)	1.00	0.92-1.08
T_{max} (h)	7.92 ± 2.73 (5.00-15.00)	7.12 ± 1.95 (5.00-12.00)	-	-
$T_{½}$	7.85 ± 2.85 (3.14-18.99)	10.32 ± 3.40 (4.87-20.90)	-	-
O-desmethylvenlafaxine				
AUC_{0-t} (ng.h/ml)	2484.28 ± 909.52 (695.76-4255.25)	2321.82 ± 768.67 (511.43-4253.62)	1.05	0.96-1.15
$AUC_{0-\infty}$ (ng.h/ml)	2587.49 ± 947.22 (722.99-4554.44)	2463.50 ± 845.49 (539.99-4941.13)	1.03	0.94-1.13
C_{max} (ng/ml)	92.50 ± 31.43 (30.79-153.00)	90.61 ± 30.17 (24.63-157.78)	1.02	0.93-1.13
T_{max} (h)	11.74 ± 4.05 (5.00-24.00)	10.14 ± 2.45 (5.00-15.00)	-	-
$T_{½}$	10.38 ± 1.86 (5.93-14.90)	11.81 ± 2.73 (7.33-18.12)	-	-

The 90% confidence intervals for the log-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for venlafaxine and the metabolite O-desmethylvenlafaxine lie within the range 80.0-125.0%.

Study BES/021/02 – Fed, 75 mg strength

In this comparative, randomised, two-way, two-period, single dose crossover study, 38 healthy fed male volunteers received 75 mg orally of either the applicant's test product or the reference product Efexor XL 75 mg 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 1 week.

Results

One subject was withdrawn prior to period II due to tonsillitis. His data were excluded from the analysis, which is satisfactory.

Bioequivalence results (mean + SD and (range)) for log-transformed test/reference ratios (ANOVA) with 90% Confidence Intervals for parent compound and active metabolite:

Test parameter	Test product	Reference product	Ratio Test/reference (geometric means)	90% ANOVA Confidence intervals
Venlafaxine				
AUC_{0-t} (ng.h/ml)	503.96 ± 334.73 (62.18-1578.54)	475.76 ± 305.58 (68.01-1445.39)	1.06	0.97-1.16
$AUC_{0-\infty}$ (ng.h/ml)	537.53 ± 329.20 (93.27-1603.06)	506.97 ± 313.72 (89.23-1465.82)	1.08	0.99-1.17
C_{max} (ng/ml)	31.77 ± 14.13 (6.04-64.80)	33.80 ± 15.96 (6.64-80.78)	0.95	0.90-1.02
T_{max} (h)	7.05 ± 2.90 (4.00-15.00)	5.51 ± 1.06 (4.00-9.00)	-	-
$T_{½}$	7.09 ± 2.43 (3.70-15.17)	9.32 ± 2.67 (5.37-18.45)	-	-

Test parameter	Test product (geometric means)	Reference product (geometric means)	Ratio Test/reference	90% Confidence intervals
O-desmethylvenlafaxine				
AUC_{0-t} (ng.h/ml)	2542.32 ± 761.41 (478.64-4728.26)	2335.17 ± 599.55 (974.94-3639.14)	1.07	0.99-1.15
$AUC_{0-\infty}$ (ng.h/ml)	2644.89 ± 796.92 (492.29-5010.37)	2466.45 ± 664.20 (1041.90-4074.64)	1.05	0.97-1.14
C_{max} (ng/ml)	97.01 ± 29.80 (24.17-168.78)	87.81 ± 21.14 (33.14-122.07)	1.08	1.03-1.14
T_{max} (h)	11.2 ± 2.81 (5.00-15.00)	9.32 ± 2.17 (5.00-15.00)	-	-
$T_{½}$	10.30 ± 2.22 (7.04-16.16)	11.76 ± 2.79 (7.61-21.01)	-	-

The 90% confidence intervals for the log-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for venlafaxine and the metabolite O-desmethylvenlafaxine lie within the range 80.0-125.0%.

Bioequivalence of 150 mg products

Study BES/022/02 – Fasted, 150 mg strength

In this comparative, randomised, two-way, two-period, single dose crossover study, 39 healthy fasted male volunteers received 150 mg orally of either the applicant's test product or the reference product Efexor XL 150 mg 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 1 week.

Results

Bioequivalence results (mean + SD and (range)) for log-transformed test/reference ratios (ANOVA) with 90% Confidence Intervals for parent compound and active metabolite:

Test parameter	Test product	Reference product	Ratio Test/reference (geometric means)	90% ANOVA Confidence intervals
Venlafaxine				
AUC_{0-t} (ng.h/ml)	1216.61 ± 822.11 (255.96-3158.06)	1090.05 ± 736.37 (229.00-2909.75)	1.11	1.01-1.21
$AUC_{0-\infty}$ (ng.h/ml)#	1280.03 ± 823.50 (281.78-3249.81)	1153.98 ± 744.99 (257.75-2974.28)	1.11	1.02-1.21
C_{max} (ng/ml)	63.03 ± 30.44 (24.51-124.10)	63.22 ± 32.98 (20.83-153.78)	1.01	0.96-1.07
T_{max} (h)	6.92 ± 2.37 (4.00-15.00)	6.42 ± 1.32 (5.00-12.00)	-	-
$T_{½}$#	7.59 ± 1.84 (3.40-12.46)	10.29 ± 2.95 (6.32-17.36)	-	-
O-desmethylvenlafaxine				
AUC_{0-t} (ng.h/ml)	4606.39 ± 1652.54 (907.35-9226.48)	4161.09 ± 1386.50 (1021.16-7324.84)	1.09	1.03-1.16
$AUC_{0-\infty}$ (ng.h/ml)	4816.86 ± 1757.74 (989.01-10153.44)	4425.71 ± 1541.15 (1060.43-8397.54)	1.08	1.02-1.14
C_{max} (ng/ml)	160.03 ± 58.16 (34.76-277.85)	148.28 ± 50.72 (33.77-240.97)	1.07	1.01-1.13
T_{max} (h)	12.01 ± 4.81 (4.00-24.00)	10.27 ± 3.22 (7.00-24.00)	-	-
$T_{½}$	9.88 ± 2.68 (6.39-16.62)	11.54 ± 3.18 (5.75-19.41)	-	-

The $AUC_{(0-\infty)}$ and T½ for Volunteer V could not be calculated, thus the presented data for these parameters are based on 38 volunteers

The 90% confidence intervals for the log-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for venlafaxine and the metabolite O-desmethylvenlafaxine lie within the range 80.0-125.0%. This is acceptable in principle.

Study BES/010/03 – Fed, 150mg strength

In this comparative, randomised, two-way, two-period, single dose crossover study, 46 healthy fed male volunteers received 150mg orally of either the applicant's test product or the reference product Efexor XL 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.

Results

Bioequivalence results [mean ± SD and (range)] for log-transformed test/reference ratios (ANOVA) with 90% Confidence Intervals for parent compound and active metabolite:

Test parameter	Test product	Reference product	Ratio Test/reference (geometric means)	90% ANOVA Confidence intervals
Venlafaxine				
AUC_{0-t} (ng.h/ml)	1020.17 ± 500.21 (162.49-2331.32)	908.79 ± 452.07 (121.04-2105.77)	1.12	1.05-1.19
$AUC_{0-\infty}$ (ng.h/ml)	1032.95 ± 499.17 (201.44-2346.27)	924.94 ± 460.49 (139.55-2239.59)	1.11	1.05-1.19

C_{max} (ng/ml)	72.46 ± 26.22 (13.00-149.00)	64.56 ± 23.58 (9.23-126.00)	1.12	1.06-1.19
T_{max} (h)*	5.53 ± 1.24 (2.00-8.50)	5.37 ± 1.04 (2.00-7.50)	-	-
$T_{½}$	5.74 ± 2.10 (3.76-15.42)	8.04 ± 2.11 (5.10-15.85)	-	-
O-desmethylvenlafaxine				
AUC_{0-t} (ng.h/ml)	4506.01 ± 1095.82 (1213.99-6330.19)	4055.68 ± 801.23 (2661.27-6045.16)	1.09	1.05-1.14
$AUC_{0-\infty}$ (ng.h/ml)	4644.12 ± 1144.85 (1235.29-6548.87)	4247.64 ± 874.78 (2746.66-6524.07)	1.08	1.04-1.12
C_{max} (ng/ml)	182.89 ± 47.95 (63.00-323.00)	154.39 ± 30.27 (98.10-237.00)	1.17	1.12-1.22
T_{max} (h)*	9.16 ± 2.56 (2.00-15.00)	7.88 ± 1.40 (5.00-12.00)	-	-
$T_{½}$	9.85 ± 1.52 (7.28-14.24)	11.04 ± 1.76 (7.47-14.72)	-	-

Assessor's overall comment on bioequivalence
The overall analyses for all four studies meet the bioequivalence criteria in accordance with CPMP criteria for both the parent compound and the active metabolite after a single dose.

In support of the application, the applicant was asked to submit an additional bioequivalence study comparing the test product with the reference product at steady state.

Study 411-DX-02-04-0000 – Fasted, 75 mg Tablets
Open, randomised, multiple dose, two-period crossover study, 30 healthy fasted male volunteers received a single daily 75 mg dose of test and reference products were administered on six consecutive days. Subjects were dosed after an overnight fast. The washout period was 16 days between the last dose in period 1 and the first dose in period 2.

Blood samples were withdrawn before each daily administration and after the final dose on day 6 hourly for the first 7 hours then at 7.5, 8, 8.5, 9, 10, 12, 15 and 24 hours. This is sufficient for adequate estimation of the PK parameters at steady state.

Statistical analyses
Conventional statistical methods and bioequivalence criteria were applied. There were no issues relating to subjects withdrawing from the study as all 30 subjects are included in the analysis.

The results for main pharmacokinetic parameters are reported as follows:

Parent drug

	Test	Reference
Css-min (ng/mL)	15.08 ± 18.31 (1.78-90.71)	15.68 ± 18.68 (4.53-97.04)
Css-max (ng/mL)	59.42 ± 36.93 (23.63-179.07)	54.33 ± 34.85 (22.92-186.44)
AUCss (ng.h/mL)	829.29 ± 692.76 (268.35-3370.48)	755.63 ± 655.97 (279.34-3256.79)
Tmax (h)*	5.80 ± 1.84 (2.00-10.00)	5.27 ± 1.23 (2.00-18.00)
% PTF*	152.61 ± 74.42 (62.92-422.47)	144.46 ± 42.62 (65.88-246.60)
Bioequivalence results for log-transformed test/reference ratios. Point estimate (90% ANOVA Confidence Interval)		
Css-min	0.88 (0.74-1.04)	
Css-max	1.09 (1.01-1.18)	
AUCss	1.11 (1.05-1.18)	

Active metabolite

	Test	Reference
Css-min (ng/mL)	82.36 ± 30.33 (23.27-141.64)	77.53 ± 25.53 (28.63-158.89)
Css-max (ng/mL)	173.33 ± 48.79 (35.24-269.40)	153.29 ± 43.13 (40.15-251.52)
AUCss (ng.h/mL)	3086.26 ± 882.78 (762.35-4852.13)	2792.93 ± 802.58 (814.52-4977.09)
Tmax (h)*	7.87 ± 2.15 (3.00-12.00)	7.67 ± 1.60 (4.00-10.00)
% PTF*	71.55 ± 24.86 (37.68-160.26)	65.19 ± 16.20 (33.94-111.96)
Bioequivalence results for log-transformed test/reference ratios. Point estimate (90% ANOVA Confidence Interval)		
Css-min	1.04 (0.95-1.14)	
Css-max	1.12 (1.08-1.17)	
AUCss	1.10 (1.06-1.15)	

PTF: Peak to trough fluctuation * non-parametric method

Assessor's comment
The 90% confidence intervals for test/reference lie within 0.80-1.25 for AUCss and Css-max. The 90% confidence intervals for Css-min are outside 0.80-1.25 but are within the pre-defined study limits of 0.70-1.43.

Assessor's Conclusions
Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated for AUCss and Css-max at steady state. All clinical and statistical aspects of the study, quality of the test and reference products and validation of the analytical method are acceptable.

Study 411-DX-03-05-0000 – Fasted, 150mg Tablets
Open, randomised, multiple dose, two-period crossover study, 35 healthy fasted male volunteers concluded in the study. A single daily 150 mg dose of test and reference products were administered on six consecutive days. Subjects were dosed after an

overnight fast. The washout period was 14 days between the last dose in period 1 and the first dose in period 2.

Blood samples were withdrawn before each daily administration and after the final dose on day 6 hourly for the first 7 hours then at 7.5, 8, 8.5, 9, 10, 12, 15 and 24 hours. This is sufficient for adequate estimation of the PK parameters at steady state.

Statistical analyses
The Results for main pharmacokinetic parameters are reported as follows:

Parent drug			
		Test	**Reference**
	C_{ss-min} (ng/mL)	38.04 ± 36.05 (1.50-169.35)	32.60 ± 25.17 (4.37-133.23)
	C_{ss-max} (ng/mL)	120.52 ± 67.40 (28.64-326.68)	106.18 ± 59.25 (21.21-280.69)
	AUC_{SS} (ng.h/mL)	1838.54 ± 1206.08 (292.72-6102.88)	1557.17 ± 978.41 (252.31-4933.52)
	T_{max} (h)*	5.43 ± 1.61 (3.00-9.00)	5.61 ± 1.03 (4.00-8.00)
	% PTF*	124.07 ± 42.86 (60.75-230.49)	122.40 ± 27.93 (66.33-192.38)
	Bioequivalence results for log-transformed test/reference ratios. Point estimate (90% ANOVA Confidence Interval)		
	C_{ss-min}	0.96 (0.81-1.15)	
	C_{ss-max}	1.13 (1.09-1.18)	
	AUC_{SS}	1.16 (1.11-1.22)	
Active metabolite			
		Test	**Reference**
	C_{ss-min} (ng/mL)	177.43 ± 58.14 (39.65-275.48)	163.70 ± 45.90 (36.91-273.47)
	C_{ss-max} (ng/mL)	332.94 ± 93.44 (160.09-506.17)	297.48 ± 73.65 (110.60-433.66)
	AUC_{SS} (ng.h/mL)	6265.75 ± 1748.28 (2927.60-9529.35)	5605.07 ± 1306.38 (2259.35-8239.83)
	T_{max} (h)*	7.89 ± 2.06 (3.00-15.00)	8.40 ± 1.85 (5.00-15.00)
	% PTF*	60.79 ± 23.81 (25.01-138.88)	57.56 ± 15.34 (29.62-89.50)
	Bioequivalence results for log-transformed test/reference ratios. Point estimate (90% ANOVA Confidence Interval)		
	C_{ss-min}	1.06 (0.97-1.16)	
	C_{ss-max}	1.11 (1.06-1.17)	
	AUC_{SS}	1.11 (1.06-1.16)	

PTF: Peak to trough fluctuation * non-parametric method

PTF: Peak to trough fluctuation * non-parametric method

Assessor's comment
The 90% confidence intervals for test/reference lie within 0.80-1.25 for AUC_{SS}, C_{SS-min} and C_{SS-max}.

Assessor's conclusions
Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated at steady state.

All clinical, statistical and pharmaceutical aspects of the study, quality of the test and reference products and validation of the analytical method are acceptable.

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 LEAFLETS (PILs)
These are satisfactory.

11. LABELLING
These are satisfactory.

12. APPLICATION FORMS (MAAs)
The MAAs are medically satisfactory.

13. SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs)
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 BENEFIT RISK ASSESSMENT

QUALITY
The important quality characteristics of ViePax XL 75 mg and 150 mg prolonged release tablets and VENLADEX XL 75 mg and 150 mg prolonged release 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence studies were carried out and the test and reference products shown to be bioequivalent for the appropriate pharmacokinetic criteria.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and labels are satisfactory and consistent with that for the UK reference products.

BENEFIT RISKASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with venlafaxine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

Viepax XL 75MG AND 150MG PROLONGED-RELEASE TABLETS

PL 14017/0118-9

VENLADEX XL 75MG AND 150MG PROLONGED-RELEASE TABLETS

PL 14017/0122-3

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 12th July 2004
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 17th May 2005 and 18th January 2007
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 28th October 2006 and 12th June 2007
5	The applications were determined on 19th November 2008

PL 14017/0118-9

VENLADEX XL 75MG AND 150MG PROLONGED-RELEASE TABLETS

PL 14017/0122-3

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

The following table lists non-safety updates to the Marketing Authorisations (PL 14017/0118-9 & 0122-3) for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
04 September 2014	Type 1B	To update section 4.1, 4.2 and 5.1 of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) in accordance with the reference products Efexor XL 75 mg and 150 mg following relevant patents expiration.	Approved 15 October 2014

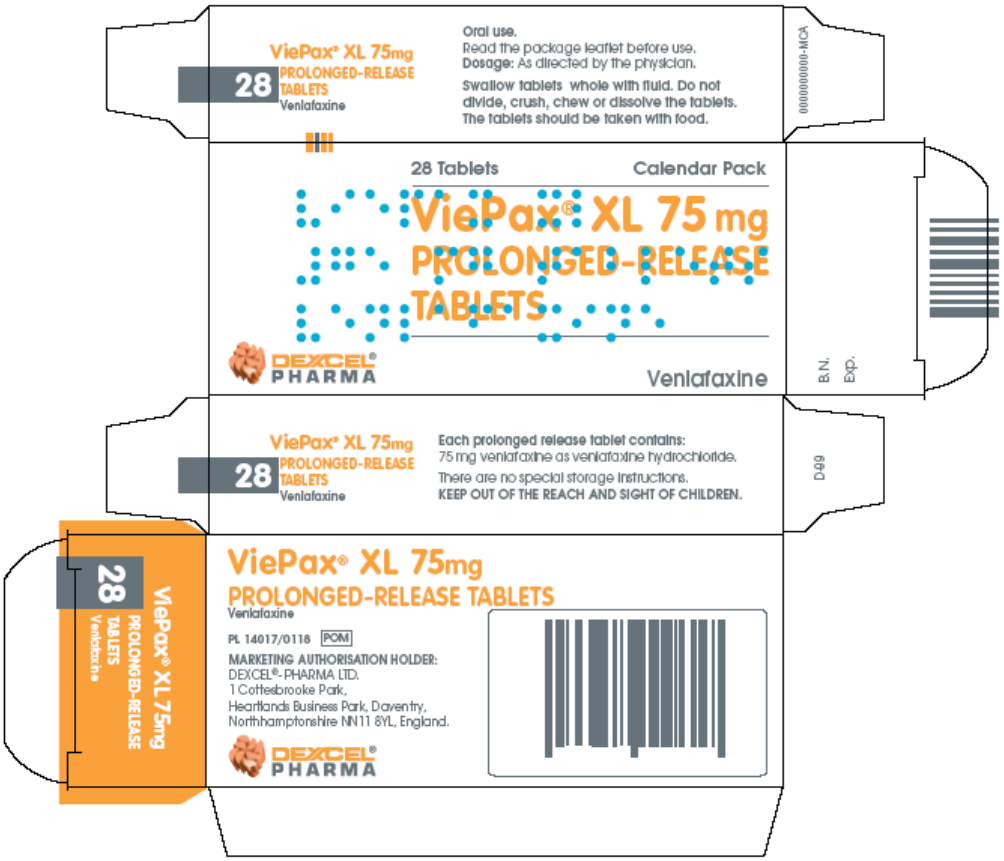
SUMMARY OF PRODUCT CHARACTERISTICS

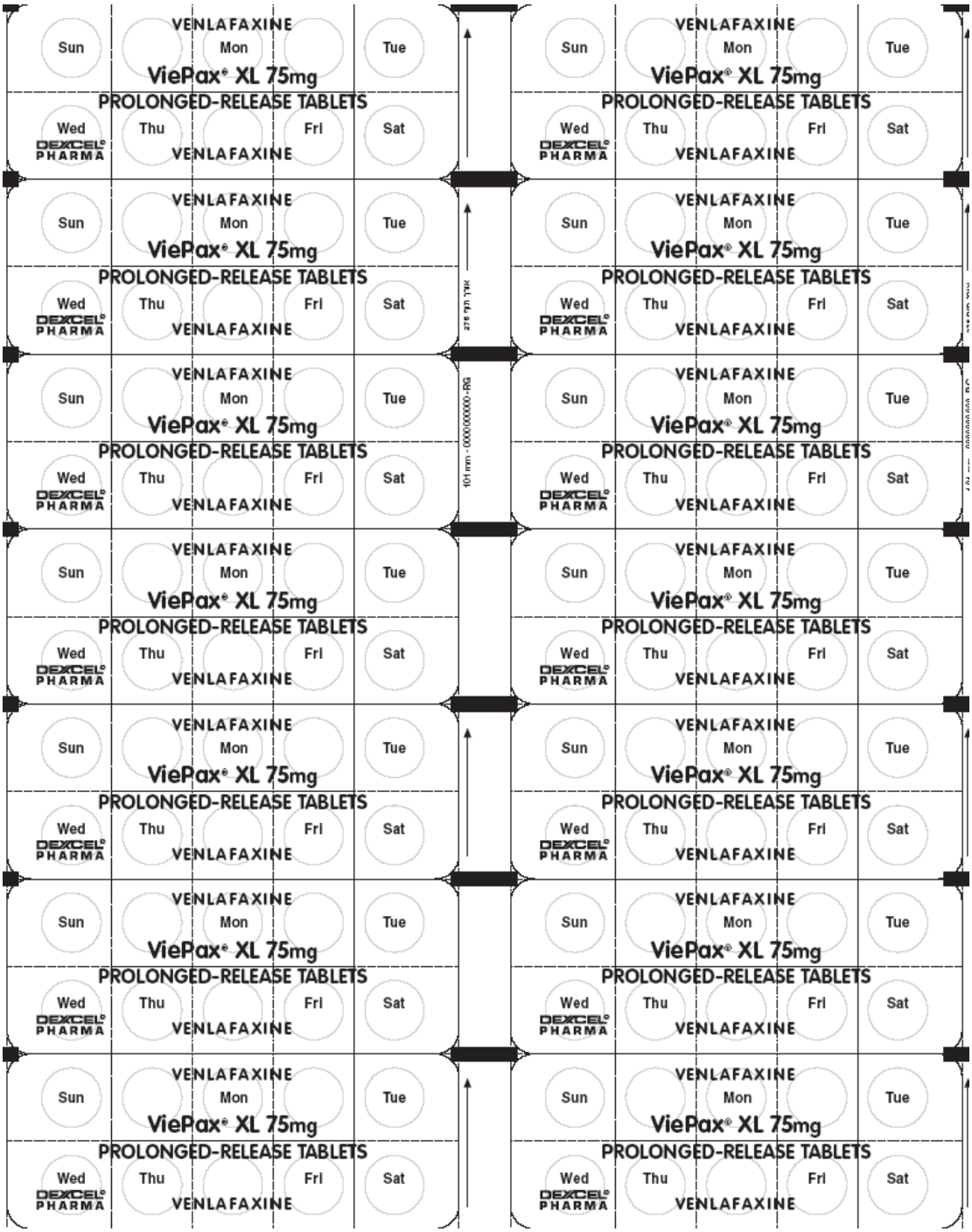
In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

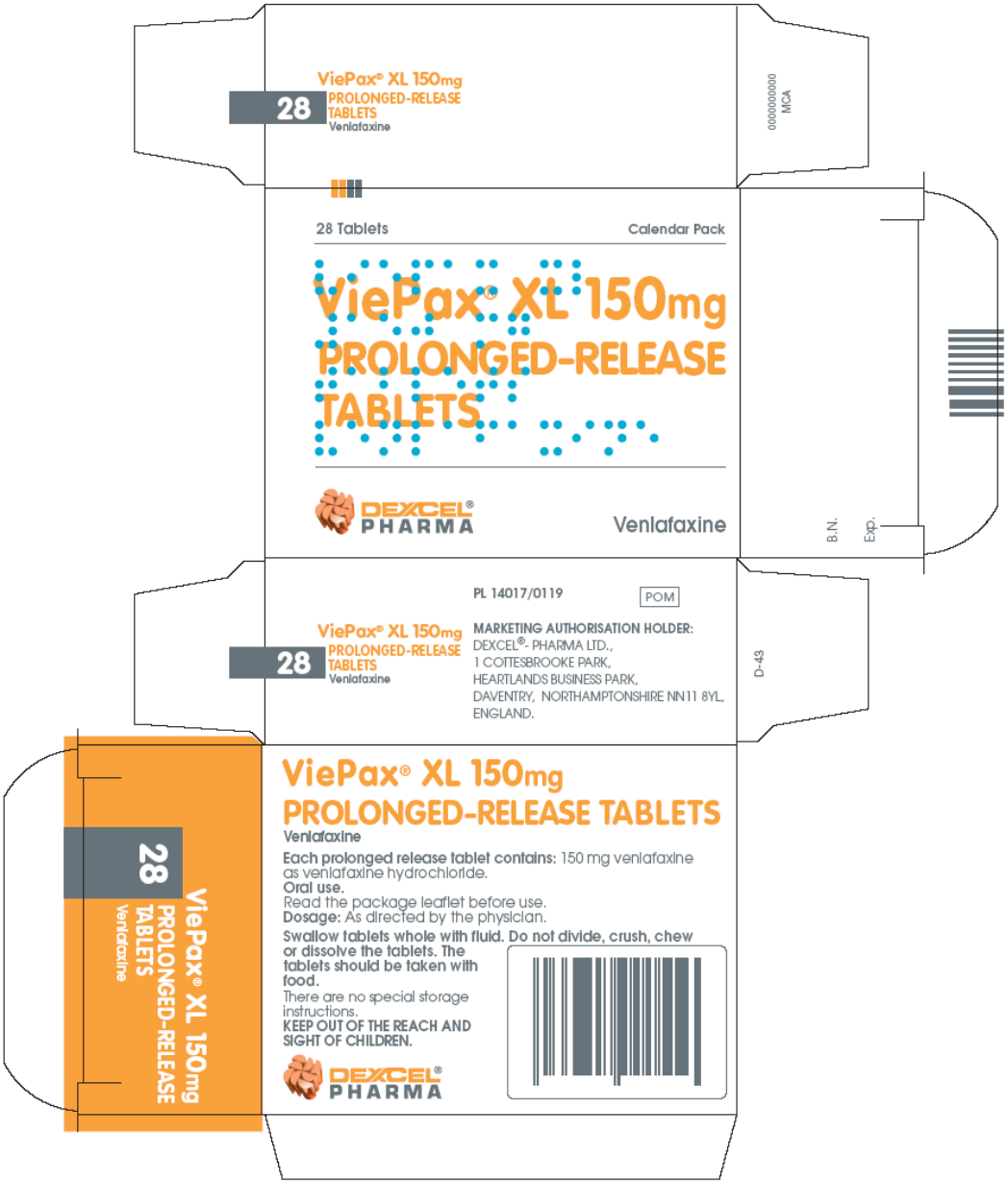
PATIENT INFORMATION LEAFLET

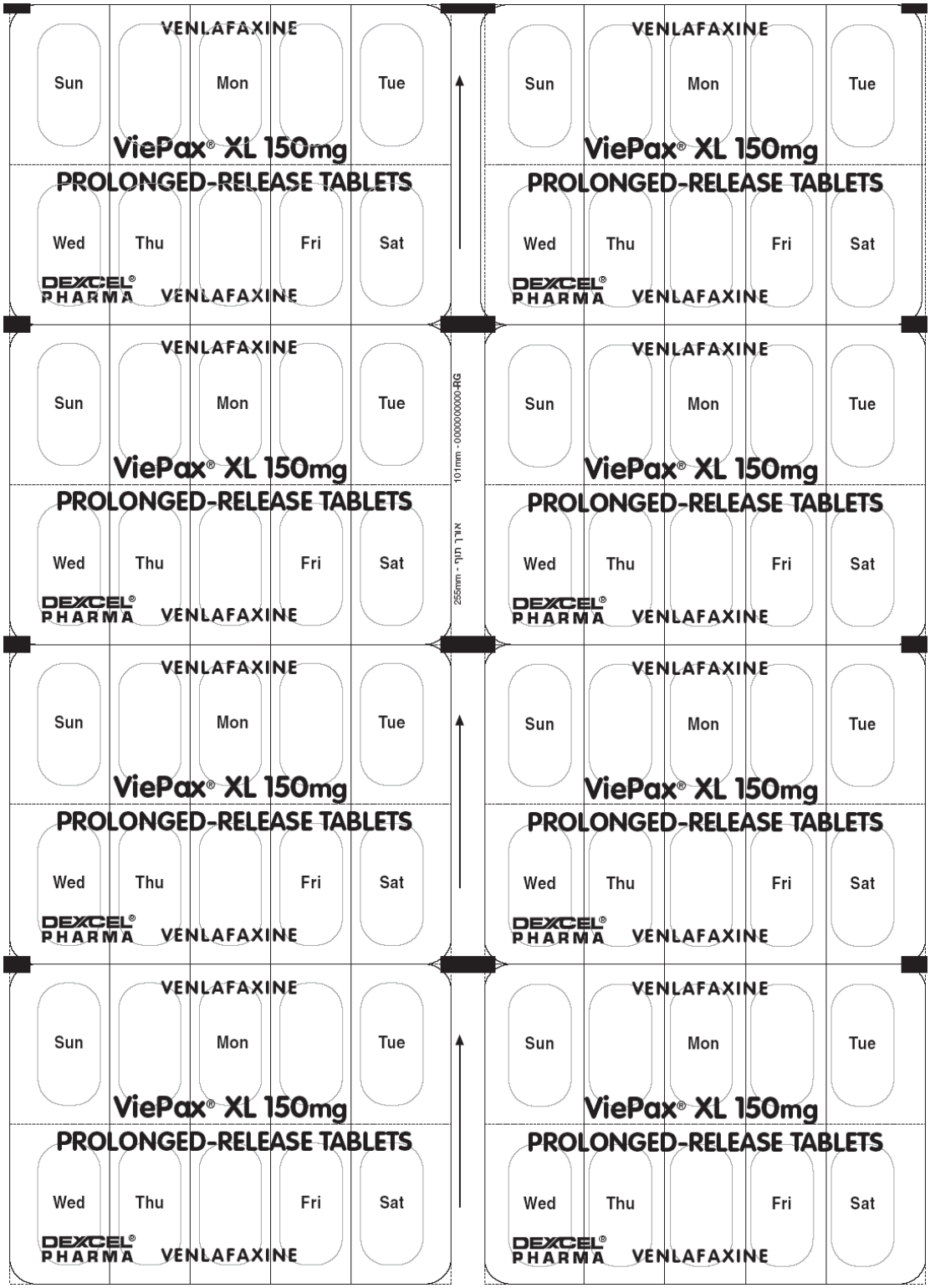
In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

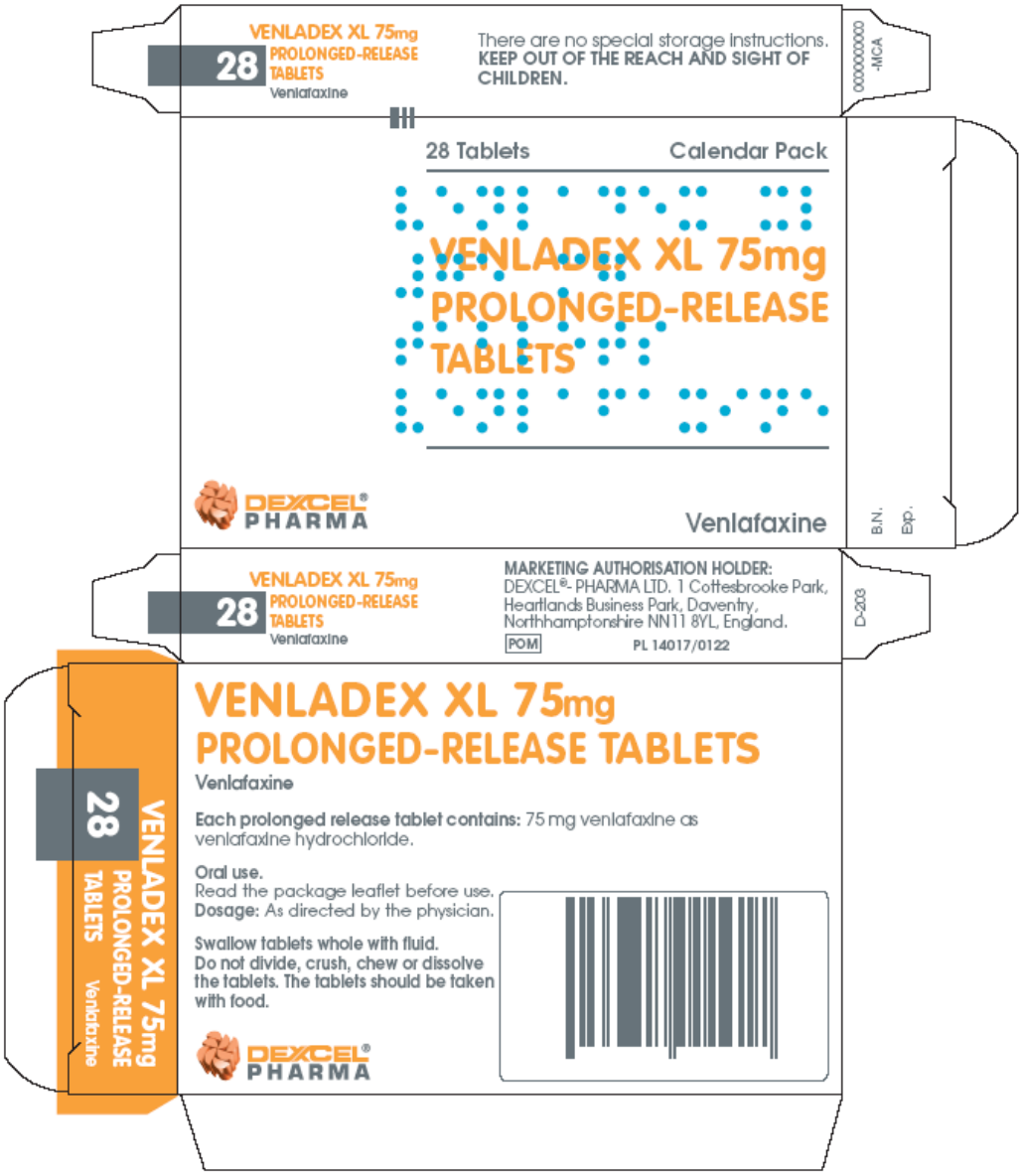
LABELLING

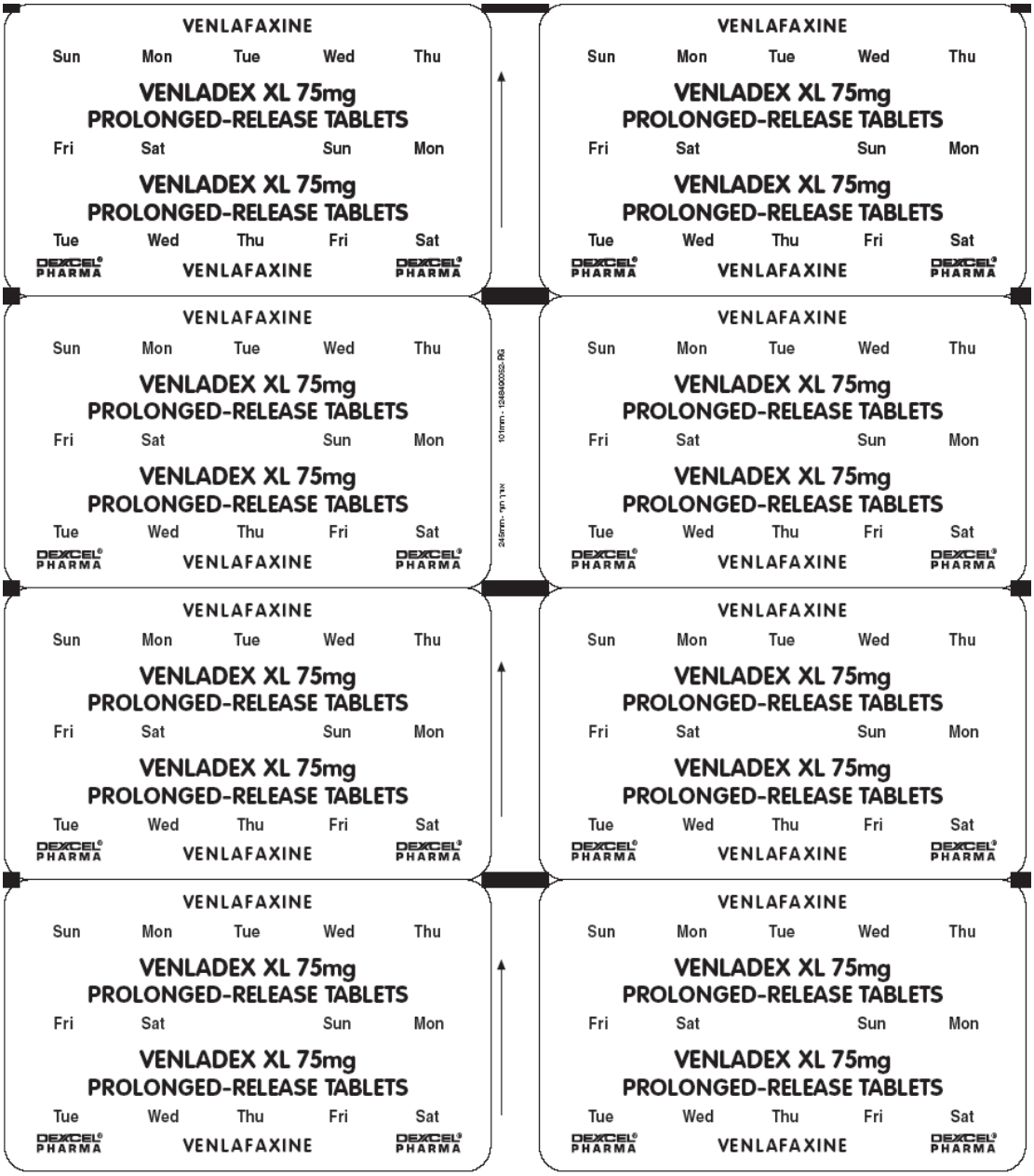

ViePax® XL 75mg
28 PROLONGED-RELEASE TABLETS
Venlafaxine
Oral use.
Read the package leaflet before use.
Dosage: As directed by the physician.
Swallow tablets whole with fluid. Do not divide, crush, chew or dissolve the tablets.
The tablets should be taken with food.
000000000-MCA
28 Tablets
Calendar Pack
ViePax® XL 75 mg
PROLONGED-RELEASE TABLETS
DEXCEL® PHARMA
Venlafaxine
B.N.
Exp.
ViePax® XL 75mg
28 PROLONGED-RELEASE TABLETS
Venlafaxine
Each prolonged release tablet contains:
75 mg venlafaxine as venlafaxine hydrochloride.
There are no special storage instructions.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
D-99
28
ViePax® XL 75mg
PROLONGED-RELEASE TABLETS
Venlafaxine
ViePax® XL 75mg
PROLONGED-RELEASE TABLETS
Venlafaxine
PL 14017/0118 POM
MARKETING AUTHORISATION HOLDER:
DEXCEL®-PHARMA LTD.
1 Cotteebrooke Park,
Heartlands Business Park, Daventry,
Northhamptonshire NN11 8YL, England.
DEXCEL® PHARMA


VENLAFAXINE
Sun
Mon
Tue
ViePax® XL 75mg
PROLONGED-RELEASE TABLETS
Wed
Thu
Fri
Sat
DEXCEL PHARMA
VENLAFAXINE


ViePax® XL 150mg
PROLONGED-RELEASE TABLETS
Venlafaxine
28
0000000000
MCA
28 Tablets
Calendar Pack
ViePax® XL 150mg
PROLONGED-RELEASE TABLETS
DEXCEL® PHARMA
Venlafaxine
B.N.
Exp.
PL 14017/0119
POM
MARKETING AUTHORISATION HOLDER:
DEXCEL®- PHARMA LTD.,
1 COITESBROOKE PARK,
HEARTLANDS BUSINESS PARK,
DAVENTRY, NORTHAMPTONSHIRE NN11 8YL,
ENGLAND.
D-43
ViePax® XL 150mg
PROLONGED-RELEASE TABLETS
Venlafaxine
Each prolonged release tablet contains: 150 mg venlafaxine as venlafaxine hydrochloride.
Oral use.
Read the package leaflet before use.
Dosage: As directed by the physician.
Swallow tablets whole with fluid. Do not divide, crush, chew or dissolve the tablets. The tablets should be taken with food.
There are no special storage instructions.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
DEXCEL® PHARMA


VENLAFAXINE
Sun
Mon
Tue
ViePax® XL 150mg
PROLONGED-RELEASE TABLETS
Wed
Thu
Fri
Sat
DEXCEL® PHARMA
VENLAFAXINE
101mm - 000000000-RG
255mm - מארז חוץ


VENLADEX XL 75mg
28
PROLONGED-RELEASE
TABLETS
Venlafaxine
There are no special storage instructions.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
28 Tablets
Calendar Pack
VENLADEX XL 75mg
PROLONGED-RELEASE
TABLETS
DEXCEL® PHARMA
Venlafaxine
B.N.
Exp.
MARKETING AUTHORISATION HOLDER:
DEXCEL®- PHARMA LTD. 1 Cottesbrooke Park,
Heartlands Business Park, Daventry,
Northhamptonshire NN11 8YL, England.
POM
PL 14017/0122
D-203
VENLADEX XL 75mg
PROLONGED-RELEASE TABLETS
Venlafaxine
Each prolonged release tablet contains: 75 mg venlafaxine as venlafaxine hydrochloride.
Oral use.
Read the package leaflet before use.
Dosage: As directed by the physician.
Swallow tablets whole with fluid.
Do not divide, crush, chew or dissolve the tablets. The tablets should be taken with food.
DEXCEL® PHARMA


VENLAFAXINE
Sun Mon Tue Wed Thu
VENLADEX XL 75mg
PROLONGED-RELEASE TABLETS
Fri Sat Sun Mon
VENLADEX XL 75mg
PROLONGED-RELEASE TABLETS
Tue Wed Thu Fri Sat
DEXCEL PHARMA
VENLAFAXINE
DEXCEL PHARMA
101mm - 124840052-R6
245mm - אורך


VENLADEX XL 150mg
28
PROLONGED-RELEASE
TABLETS
Venlafaxine
00000000
MCA
28 Tablets
Calendar Pack
VENLADEX XL 150mg
PROLONGED-RELEASE
TABLETS
DEXCEL®
PHARMA
Venlafaxine
Exp.
B.N.
VENLADEX XL 150mg
28
PROLONGED-RELEASE
TABLETS
Venlafaxine
POM
PL 14017/0123
MARKETING AUTHORISATION HOLDER:
DEXCEL®- PHARMA LTD., 1 COTTESBROOKE PARK,
HEARTLANDS BUSINESS PARK, DAVENTRY,
NORTHAMPTONSHIRE NN11 8YL, ENGLAND.
D-26
VENLADEX XL 150mg
PROLONGED-RELEASE TABLETS
Venlafaxine
Each prolonged release tablet contains: 150 mg venlafaxine as venlafaxine hydrochloride.
Oral use.
Read the package leaflet before use.
Dosage: As directed by the physician.
Swallow tablets whole with fluid. Do not divide, crush, chew or dissolve the tablets. The tablets should be taken with food.
There are no special storage instructions.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
DEXCEL®
PHARMA
28
VENLADEX XL 150mg
PROLONGED-RELEASE
TABLETS
Venlafaxine


VENLAFAXINE
Sun Mon Tue Wed Thu Fri Sat
VENLADEX XL 150mg
PROLONGED-RELEASE TABLETS
Sun Mon Tue Wed Thu Fri Sat
DEXCEL® PHARMA
VENLAFAXINE
VENLAFAXINE
Sun Mon Tue Wed Thu Fri Sat
VENLADEX XL 150mg
PROLONGED-RELEASE TABLETS
Sun Mon Tue Wed Thu Fri Sat
DEXCEL® PHARMA
VENLAFAXINE
VENLAFAXINE
Sun Mon Tue Wed Thu Fri Sat
VENLADEX XL 150mg
PROLONGED-RELEASE TABLETS
Sun Mon Tue Wed Thu Fri Sat
DEXCEL® PHARMA
VENLAFAXINE
VENLAFAXINE
Sun Mon Tue Wed Thu Fri Sat
VENLADEX XL 150mg
PROLONGED-RELEASE TABLETS
Sun Mon Tue Wed Thu Fri Sat
DEXCEL® PHARMA
VENLAFAXINE

ANNEX 1

Our Reference: PL 14017/0118-0036
PL 14017/0119-0031
PL 14017/0122-0033
PL 14017/0123-0029

Product: ViePax XL 75 mg prolonged-release tablets
ViePax XL 150 mg prolonged-release tablets
VENLADEX XL 75 mg prolonged-release tablets
VENLADEX XL 150 mg prolonged-release 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 section 4.1, 4.2 and 5.1 of the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) in accordance with the reference products Efexor XL 75 mg and 150 mg following relevant patents expiration.

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

Evaluation
The proposed changes to the SmPCs and PILs are in line with the product information for Efexor XL 75 mg & 150 mg (the brand leader).

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

Decision - Approved on 15 October 2014.