Public Assessment Report

Depefex 75 mg and 150 mg XL Capsules (venlafaxine hydrochloride)

Procedure No: UK/H/1004/001-2/DC

UK Licence No.: PL 08829/0171-0172

Chiesi Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY
Depefex 75 mg and 150 mg XL Capsules
(venlafaxine hydrochloride)

This is a summary of the public assessment report (PAR) for Depefex 75 mg and 150 mg XL Capsules (PL 08829/0171-0172; UK/H/1004/001-02/DC). These products will be referred to as Depefex Capsules in the remainder of the summary, for ease of reading.

This summary explains how Depefex Capsules were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Depefex Capsules.

For practical information about Depefex Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Depefex Capsules and what are they used for?

Depefex Capsules are 'generic medicines'. This means that Depefex Capsules are similar to 'reference medicines' already authorised in the UK called Efexor XL 75 mg and 150 mg prolonged-release capsules, hard (John Wyeth and Brother Limited; PL 00011/0223-0224).

Depefex Capsules are used for the treatment of depression.

How are Depefex Capsules used?

Depefex Capsules are taken by mouth. The capsules should be swallowed whole at approximately the same time each day, either in the morning or evening. The patient should not break open, crush or chew the capsules, or put them in water before swallowing. Depefex Capsules should be taken with food.

The usual starting dose is one 75 mg capsule a day. However, a doctor may start with a different dose, particularly if the patient is an elderly or has liver or kidney problems. A doctor may also change the dose during the course of the treatment. The dose can be raised by a doctor gradually, and if needed, even up to a maximum dose of 375 mg daily for depression.

These medicinal products can only be obtained on prescription from a doctor.

For further information on how Depefex Capsules are used, refer to the Summaries of Product Characteristics or package leaflet available on the MHRA website.

How do Depefex Capsules work?

Depefex Capsules contain the active substance venlafaxine, which belongs to a group of medicines known as antidepressants. They are one of a group of medicines called a selective serotonin and noradrenaline reuptake inhibitor (SNRI). 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.

How have Depefex Capsules been studied?
Because Depefex Capsules are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Efexor XL 75 mg and 150 mg Capsules (John Wyeth and Brother Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Depefex Capsules?
As Depefex Capsules are generic medicines that are bioequivalent to the reference medicines, Efexor XL 75 mg and 150 mg Capsules, their benefits and risks are taken as being the same as those for the reference medicines.

Why are Depefex Capsules approved?
It was concluded that, in accordance with EU requirements, Depefex Capsules have been shown to have comparable quality and to be bioequivalent to Efexor XL 75 mg and 150 mg Capsules. Therefore, the view was that, as for Efexor XL 75 mg and 150 mg Capsules, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Depefex Capsules?
A satisfactory pharmacovigilance system has been provided to ensure that Depefex Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Depefex Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Depefex Capsules
Republic of Ireland and the UK agreed to grant Marketing Authorisations for Tardcaps 75 mg and 150 mg XL Capsules (PL 17659/0009-0010; UK/H/1004/001-02/DC) on 28th October 2007. Marketing Authorisations were granted in the UK on 15th February 2008.

Subsequent to a change of ownership procedure, the Marketing Authorisations Tardcaps 75 mg and 150 mg XL Capsules (PL 17659/0009-0010; UK/H/1004/001-02/DC) were granted to Chiesi Limited (PL 08829/0171-0172; UK/H/1004/001-02/DC) on 2nd March 2010.

The product names of Tardcaps 75 mg and 150 mg XL Capsules were changed to the current product names, Depefex 75 mg and 100 mg XL Capsules on 12th April 2010.

For more information about taking Depefex Capsules, read the Patient Information Leaflet (PIL), or contact your doctor or pharmacist.

The full PAR for Depefex Capsules follows this summary.

This summary was last updated in July 2015.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Depefex 75 mg and 150 mg XL Capsules could be approved. The products are prescription-only medicines for the treatment of major depressive episodes and for prevention of recurrence of major depressive episodes.

These are applications made under the decentralised procedures (DCP), according to Article 10.1 of 2001/83 EC, as amended, claiming to be a generic medicinal products of Efexor 75 mg and 150 mg Tablets (PL 00011/0223-0224; Wyeth Laboratories, UK) which were granted UK licences over 10 years ago.

The active ingredient, venlafaxine hydrochloride, is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents. 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. Non-clinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products prior to granting authorisation.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Subsequent to a change of ownership procedure, the Marketing Authorisations Tardcaps 75 mg and 150 mg XL Capsules (PL 17659/0009-0010; UK/H/1004/001-02/DC) were granted to Chiesi Limited (PL 08829/0171-0172; UK/H/1004/001-02/DC) on 2nd March 2010.

The product names of Tardcaps 75 mg and 150 mg XL Capsules were changed to the current product names, Depefex 75 mg and 100 mg XL Capsules on 12th April 2010.

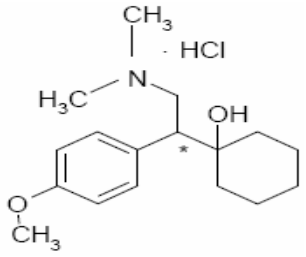
II QUALITY ASPECTS
DRUG SUBSTANCE

General Information

Nomenclature
INN/Ph.Eur name: Venlafaxine Hydrochloride

Chemical name: 1-2[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol
(±)-1-[a-[dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol
N,N-dimethyl-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethylamine

Structural formula:



Molecular formula: $C_{17}H_{27}NO_2HCl$
Molecular weight: 313.9 g/mol

Appearance: White or almost white powder
Solubility: Freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone.

Venlafaxine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of venlafaxine hydrochloride are supported by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability. This certificate is accepted as confirmation of the suitability of venlafaxine hydrochloride for inclusion in the medicinal product.

Active venlafaxine hydrochloride is packaged into a transparent polyethylene bag, which is covered by an outer grey polyethylene bag. Both are sealed with polyamide cable ties and the bags are placed into fibreboard drums. Satisfactory specifications have been provided for all packaging. The primary packaging has been shown to comply with current legislation concerning contact with food.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a retest period of 3 years with the storage precautions ‘Store in a well-closed container’ and ‘Protect from light’. Suitable post approval stability commitments have been made to follow these studies up to 5 years and to place a new batch on stability every 12 months.

DRUG PRODUCT
Other Ingredients

Other ingredients consist of pharmaceutical excipients stearic acid, ethylcellulose, talc, sugar spheres 20 (which consist of maize starch and sucrose) and the capsule shell (which consists of gelatin and titanium dioxide).

All excipients comply with their European Pharmacopoeia monograph, with the exception of the capsule shell (which complies with a suitable in-house specification). None of the excipients contain materials of animal or human origin, except gelatin in the capsule shell. The suppliers of gelatin have provided EDQM Certificates of Suitability to show that they are in compliance with current regulations concerning the minimising of transmission of BSE/TSE. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System
Both strengths of tablets are packaged in aluminium/polyvinylchloride/polyvinyldene chloride blisters contained in cardboard boxes. Pack sizes for both strengths are 28 capsules.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with the storage conditions ‘Do not store above 25°C’ and ‘Store in the original package’.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies and to place the next two commercial-scale batches of each strength on stability.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Conclusion
The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of venlafaxine hydrochloride are well-known. Therefore, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

There are no objections to the approval of these products from a non-clinical point of view.

IV CLINICAL ASPECTS

Pharmacokinetics
The pharmacokinetics of venlafaxine is well-described. It is well-absorbed (>92%) and undergoes extensive first-pass metabolism. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172 ng/ml after 25 to 150 mg 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 (activity similar to the parent). The mean disposition half-life of venlafaxine and O-desmethylvenlafaxine is approximately 5 and 11 hours, respectively. Both the parent drug venlafaxine and the active metabolite O-desmethylvenlafaxine were assayed in all bioequivalence studies; this is appropriate.

Clinical Pharmacology
With the exception of the three bioequivalence studies comparing Tardcaps 150 mg XL Capsules versus Efexor XL 150 mg Capsules, no formal data are provided and none are required for these applications.

Study 132: An open-label, comparative, single-dose, randomised, two-period, crossover bioavailability study in healthy adult subjects under fed conditions comparing Tardcaps 150 mg XL Capsules versus Efexor XL 150 mg Capsules

All subjects fasted overnight and were given a high-fat, high-calorie breakfast 30 minutes before dosing. Blood samples were taken pre- and up to 36 hours post dose, with a washout period of 7 days.

Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values and geometric means:

Treatment	**AUC_{0-t} (ng/ml/h)**	**$AUC_{0-\infty}$ (ng/ml/h)**	**C_{max} (ng/ml)**
Venlafaxine hydrochloride:			
Test	1725	1851	130
Reference	1571	1769	116
Ratio (90% CI)	1.10 (1.02; 1.18)	1.05 (0.97; 1.13)	1.12 (1.02; 1.22)
O-desmethylvenlafaxine:			
Test	4672	4798	201
Reference	4475	4679	170
Ratio (90% CI)	1.04 (1.00; 1.09)	1.03 (0.99; 1.07)	1.19 (1.11; 1.27)

Study 133: An open-label, comparative, single-dose, randomised, two-period, crossover bioavailability study in healthy adult subjects under fasted conditions comparing Tardcaps 150 mg XL Capsules versus Efexor XL 150 mg Capsules

All subjects fasted overnight before dosing. Blood samples were taken pre- and up to 36 hours post dose, with a washout period of 7 days.

Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values and geometric means:

Treatment	**AUC_{0-t} (ng/ml/h)**	**$AUC_{0-\infty}$ (ng/ml/h)**	**C_{max} (ng/ml)**
Venlafaxine hydrochloride:			
Test	1311	1412	94.9
Reference	1270	1411	87.7
Ratio (90% CI)	1.03 (0.98; 1.09)	1.00 (0.95; 1.06)	1.08 (1.03; 1.14)
O-desmethylvenlafaxine:			
Test	6423	6617	245
Reference	6266	6500	221
Ratio (90% CI)	1.03 (0.99; 1.06)	1.02 (0.99; 1.05)	1.11 (1.07; 1.15)

Study 134: An open-label, comparative, multiple-dose, randomised, two-period, crossover bioavailability study in healthy adult subjects under fed conditions comparing Tardcaps 150mg XL Capsules versus Efexor XL 150mg Capsules

This study consisted of two treatment phases each of 4 days, starting with a run-in period of 3 days (Days 1 to 3) during which subject received their randomised treatment every 24 hours, followed by a profile period of 24 hours (Days 4 to 5) and a drug-free period of 8 days between treatment phases. A standardised meal was given 5 minutes after administration of study medication.

Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values and geometric means:

Treatment	AUC_{0-t} (ng/ml/h)	C_{max} (ng/ml)	C_{min} (ng/ml)	PTF%
Venlafaxine hydrochloride:				
Test	1821	137	30.2	139
Reference	1710	128	34.1	129
Ratio (90% CI)	1.07 (1.02; 1.13)	1.08 (1.02; 1.14)	89.0 (83.3; 95.2)	1.08 (1.04; 1.12)
O-desmethylvenlafaxine:				
Test	6031	317	170	56.9
Reference	5858	303	172	52.5
Ratio (90% CI)	1.03 (1.01; 1.06)	1.05 (1.02; 1.07)	98.9 (95.7; 1.02)	1.08 (1.04; 1.13)

With the exception of the comparison of C_{max} for O-desmethylvenlafaxine in the single-dose fed study (Study 132), all other parameters were within the accepted range for bioequivalence to have been demonstrated between the two products. Further investigation of the reasons behind the C_{max} value for O-desmethylvenlafaxine in Study 132, where the upper limit was slightly outside the accepted range, found that there were two subjects whose blood samples had been incorrectly taken at one timepoint post dose. It was considered suitable to remove these subjects and recalculation of C_{max} based on their removal brought the values in-line with the accepted range (1.09-1.22).

As the two strengths of the proposed product meet all the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 150 mg strength can be extrapolated to the 75 mg strength.

Efficacy
No new data on the efficacy of venlafaxine hydrochloride are submitted and none are required for these types of application.

Safety
No new data on the safety of venlafaxine hydrochloride are submitted and none are required for these types of application.

SmPC, PIL, Labels

The SmPC, PIL and Labels are medically acceptable. The SmPC is consistent with that for the originator products.

Conclusion
The grant of Marketing Authorisations is recommended.

V. USER CONSULTATION

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, as amended. The language used for the purpose of user testing the package leaflet was English.

The package leaflet meets the criteria for readability as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use.*

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

Quality
The important quality characteristics of Depefex 75 mg and 150 mg XL Capsules 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.

Clinical
Bioequivalence has been demonstrated between the applicant's Tardcaps 150 mg XL Capsules and the originator products Efexor 150 mg Capsules (Wyeth Laboratories UK). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 150 mg strength can be extrapolated to the 75 mg strength tablets.

No new or unexpected safety concerns arose from these applications.

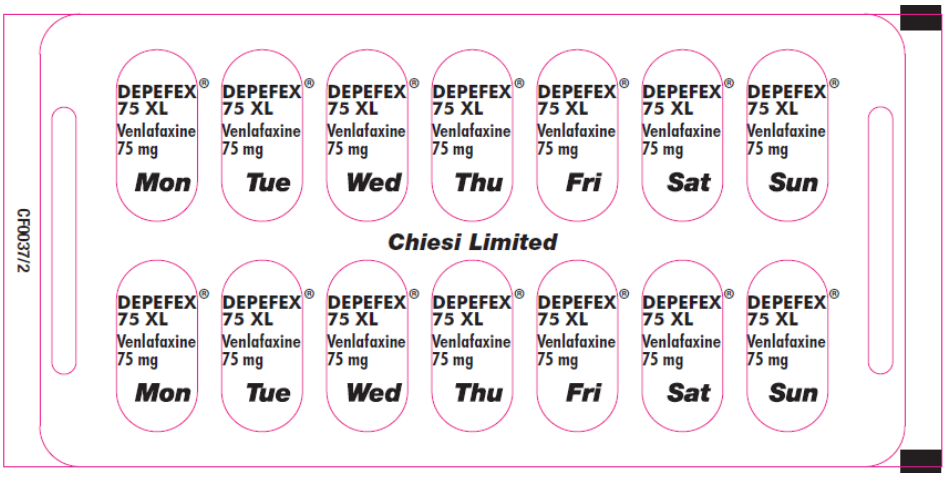
The SmPC, PIL and labelling are satisfactory and consistent with that for Efexor Capsules.

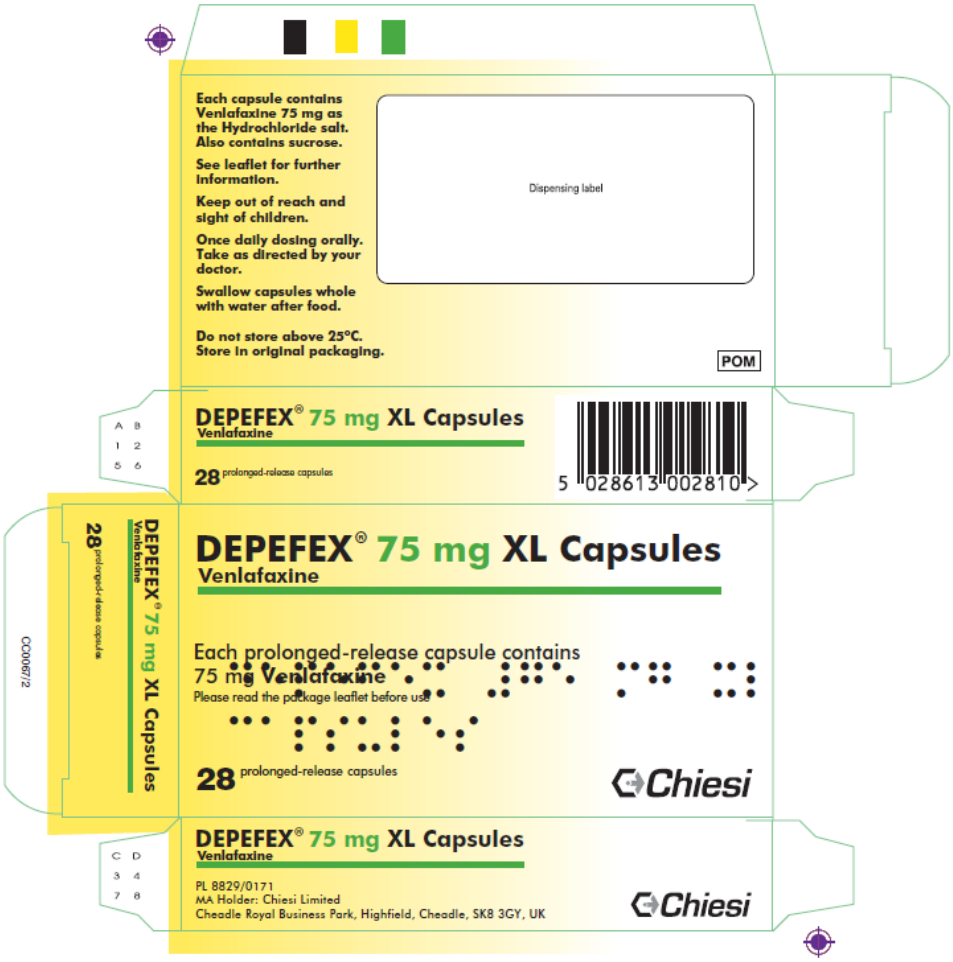
Benefit Risk Assessment
The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with venlafaxine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

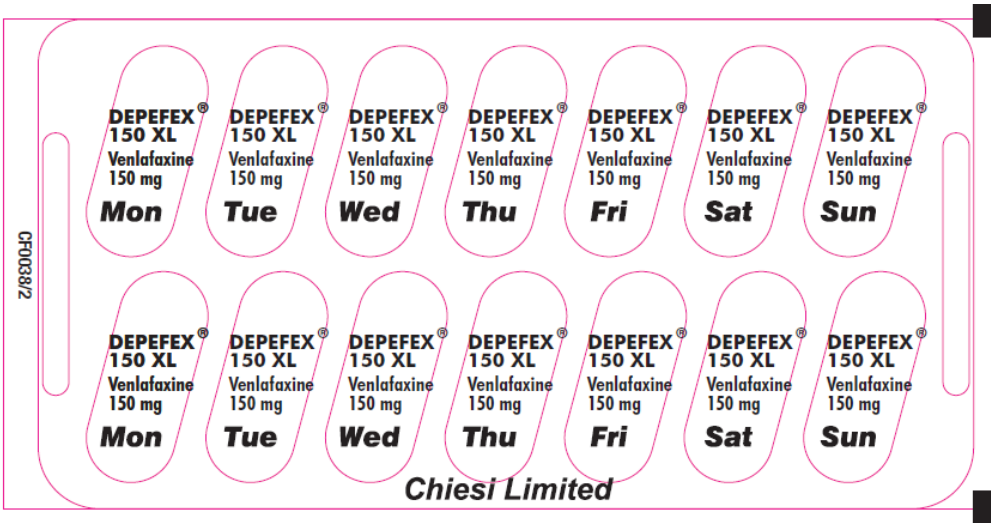
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

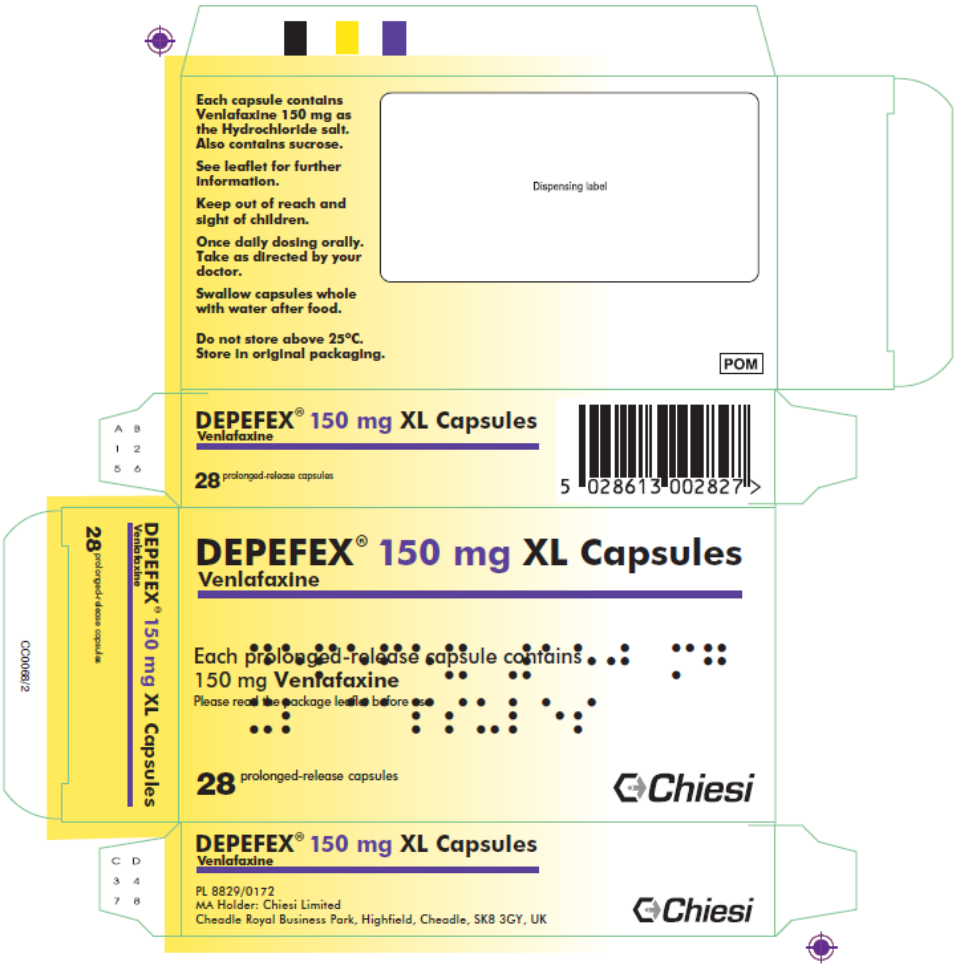
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING




Each capsule contains Venlafaxine 75 mg as the Hydrochloride salt. Also contains sucrose.
See leaflet for further information.
Keep out of reach and sight of children.
Once daily dosing orally. Take as directed by your doctor.
Swallow capsules whole with water after food.
Do not store above 25°C. Store in original packaging.
Dispensing label
POM
DEPEFEX® 75 mg XL Capsules
Venlafaxine
28 prolonged-release capsules
5 028613 002810
A B 1 2 5 6
C D 3 4 7 8
CC0067/2
DEPEFEX® 75 mg XL Capsules
Venlafaxine
28 prolonged-release capsules
Each prolonged-release capsule contains 75 mg Venlafaxine
Please read the package leaflet before use
28 prolonged-release capsules
Chiesi
PL 8829/0171
MA Holder: Chiesi Limited
Cheadle Royal Business Park, Highfield, Cheadle, SK8 3GY, UK


CF0038/2
DEPEFEX® 150 XL Venlafaxine 150 mg Mon
DEPEFEX® 150 XL Venlafaxine 150 mg Tue
DEPEFEX® 150 XL Venlafaxine 150 mg Wed
DEPEFEX® 150 XL Venlafaxine 150 mg Thu
DEPEFEX® 150 XL Venlafaxine 150 mg Fri
DEPEFEX® 150 XL Venlafaxine 150 mg Sat
DEPEFEX® 150 XL Venlafaxine 150 mg Sun
Chiesi Limited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Once daily dosing orally. Take as directed by your doctor.
Swallow capsules whole with water after food.
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Dispensing label
POM
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Venlafaxine
28 prolonged-release capsules
5 028613 002827
A B 1 2 5 6
DEPEFEX® 150 mg XL Capsules
Venlafaxine
28 prolonged-release capsules
CD0068/2
DEPEFEX® 150 mg XL Capsules
Venlafaxine
Each prolonged-release capsule contains 150 mg Venlafaxine
Please read the package leaflet before use
28 prolonged-release capsules
Chiesi
DEPEFEX® 150 mg XL Capsules
Venlafaxine
PL 8829/0172
MA Holder: Chiesi Limited
Cheadle Royal Business Park, Highfield, Cheadle, SK8 3GY, UK
Chiesi
C D 3 4 7 8

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists a non-safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the 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
1st May 2015	Type IB	To update sections 2, 4.2, 4.3 and 4.8 of the SmPCs in line with the quality review of Documents (QRD) template. Consequently, the PIL has been updated.	Approved on 29th June 2015

Annex 1

Reference: **PL 08829/0171-0042; PL 08829/0172-0041;**

Product: **Depefex 75 mg and 150 mg XL Capsules**

MAH: **Chiesi Limited**

Active Ingredient: **venlafaxine hydrochloride**

Reason:
To update sections 2, 4.2, 4.3 and 4.8 of the SmPCs in line with the QRD template. Consequently, the PIL has been updated.

Supporting evidence
The applicant has submitted updated sections of the SmPCs and the leaflet.

Evaluation
The amended sections of the SmPCs and the leaflet mock-up are satisfactory.

Conclusion
The variations were approved on 29th June 2015 and the updated SmPC fragments and the PIL have been incorporated into these Marketing Authorisations. The proposed changes are acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) – Updated

Following approval of the variations on 27th June 2015 the SmPCs were updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET (PIL) - Updated

Following approval of the variations on 29th June 2015 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.