

**Venlafaxine 37.5 mg Tablets
Venlafaxine 75 mg Tablets
(venlafaxine hydrochloride)**

PL 30306/0216 and PL 30306/0218

UK Public Assessment Report

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Venlafaxine 37.5 mg Tablets Venlafaxine 75 mg Tablets

(venlafaxine hydrochloride)

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Venlafaxine 37.5 mg Tablets (PL 30306/0216, formerly PL 08608/0075) and Venlafaxine 75 mg Tablets (PL 30306/0218 formerly PL 08608/0077). It explains how the applications for Venlafaxine 37.5 mg and 75 mg Tablets were assessed and their authorisations recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Venlafaxine 37.5 mg and 75 mg Tablets.

For practical information about using Venlafaxine 37.5 mg and 75 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The products may be referred to as 'Venlafaxine Tablets' in this report.

What are Venlafaxine Tablets and what are they used for?

Venlafaxine 37.5 mg and 75 mg Tablets are generic medicines. This means that Venlafaxine 37.5 mg and 75 mg Tablets are similar to 'reference medicines' already authorised in the UK called Efexor 37.5 mg and 75 mg Tablets, which were authorised to John Wyeth and Brother Limited on 27 November 1994.

Venlafaxine Tablets are used to treat adults with depression. Treating depression properly is important. If it is not treated, the condition may not go away and may become more serious and more difficult to treat.

How do Venlafaxine Tablets work?

Venlafaxine 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 anxiety disorders in adults. 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 Venlafaxine Tablets used?

Venlafaxine Tablets are taken by mouth. The tablets should be taken approximately at the same time each day, in the morning and in the evening, with food.

Venlafaxine tablets should always be taken as instructed by the doctor. If unsure, the patient should check with his/her doctor or pharmacist.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Venlafaxine Tablets can only be obtained with a prescription.

What benefits of Venlafaxine Tablets have been shown in studies?

As Venlafaxine 37.5 mg and 75 mg Tablets are generic medicines, studies in patients have been limited to tests to determine that Venlafaxine 37.5 mg and 75 mg Tablets are bioequivalent to the reference medicines, Efexor 37.5 mg and 75 mg Tablets (Wyeth Laboratories, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder, Olinka UK Limited, has provided data from the published literature on venlafaxine.

What are the possible side effects of Venlafaxine Tablets?

Like all medicines, Venlafaxine Tablets can cause side effects although not everybody gets them.

For the full list of all side effects reported with Venlafaxine Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Venlafaxine Tablets approved?

It was concluded that, in accordance with EU requirements, Venlafaxine 37.5 mg and 75 mg Tablets have been shown to have comparable quality and to be comparable to Efexor 37.5 mg and 75 mg Tablets (Wyeth Laboratories, UK). Therefore, the MHRA decided that, as for Efexor 37.5 mg and 75 mg Tablets (Wyeth Laboratories, UK), the benefits outweigh the identified risks and recommended that Venlafaxine 37.5 mg and 75 mg Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Venlafaxine Tablets?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Venlafaxine 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.

Other information about Venlafaxine Tablets

Marketing Authorisations (Venlafaxine 37.5 mg Tablets (PL 08608/0075) and Venlafaxine 75 mg Tablets (PL 08608/0077)) were first granted in the UK to Olinka UK Limited on 17 September 2008.

Subsequent to Change of Ownership procedures, the Marketing Authorisations Venlafaxine 37.5 mg Tablets (PL 30306/0216) and Venlafaxine 75 mg Tablets (PL 30306/0218) were granted in the UK to Actavis Group PTC ehf on 17 November 2008.

The full PAR for Venlafaxine Tablets follows this summary.

For more information about treatment with Venlafaxine Tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.

VENLAFAXINE 37.5 MG TABLETS
VENLAFAXINE 75 MG TABLETS
(venlafaxine hydrochloride)

SCIENTIFIC DISCUSSION

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SCIENTIFIC DISCUSSION

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Olinka UK Limited Marketing Authorisations for the medicinal products Venlafaxine 37.5 mg Tablets (PL 08608/0075) and Venlafaxine 75 mg Tablets (PL 08608/0077) on 17 September 2008. These are prescription-only medicines (POM).

These national, abridged applications are for two strengths of immediate-release film-coated tablets containing 37.5 mg and 75 mg of the serotonin and noradrenaline re-uptake inhibitor (SNRI) venlafaxine. The applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal versions of the UK reference products, Efexor 37.5 mg and 75 mg Tablets (PL 00011/0198 & 0201) respectively, authorised to John Wyeth and Brother Limited on 27 November 1994. The innovator products, Efexor 37.5 mg and 75 mg Tablets, granted to Wyeth Pharmaceuticals BV (Netherlands) in June 1994, have been authorised in the EU for more than 10 years, so the period of data exclusivity has expired.

The active ingredient, venlafaxine hydrochloride, belongs to the pharmacotherapeutic group of drugs called 'other antidepressants'. Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. These products are indicated for the treatment of depressive illness including depression accompanied by anxiety. Following an initial response venlafaxine is indicated for the prevention of relapses of the initial episode of depression or for the prevention of the recurrence of new episodes.

These applications for Venlafaxine 37.5 mg and 75 mg Tablets both depend on the single bioequivalence study presented comparing the applicant's 37.5 mg product with the UK reference product Efexor 37.5 mg Tablets. Consequently, all sections of the Scientific Discussion refer to both strengths of products. As the test products, Venlafaxine 37.5 mg and 75 mg Tablets, were deemed to meet 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 study on the 37.5 mg strength were extrapolated to the 75 mg strength tablet strength.

Subsequent to Change of Ownership procedures, the Marketing Authorisations Venlafaxine 37.5 mg Tablets (PL 30306/0216) and Venlafaxine 75 mg Tablets, PL 30306/0218) were granted in the UK to Actavis Group PTC ehf on 17 November 2008.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The drug products are presented as orange, round, biconvex, film-coated tablets containing 37.5 mg or 75 mg of venlafaxine base (see Summary of Product Characteristics (SmPCs)/patient information leaflet for full descriptions of tablets).

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, povidone K30, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate making up the tablet core; and titanium dioxide (E171), hypromellose 6 cP, macrogol 400, and sunset yellow FCF lake (E110) constituting 'Opadry 03B23319 Orange' which makes up the tablet coating. Appropriate justification for the inclusion of each excipient has been provided.

The finished products are marketed in PVC (polyvinylchloride)/aluminium blister strips, or in high density polyethylene (HDPE) containers with low density polyethylene (LDPE) screw caps; either of which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The products are packaged in pack sizes of 14, 28, 30, 42 and 56 film-coated tablets. The Marketing Authorisation Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Venlafaxine hydrochloride

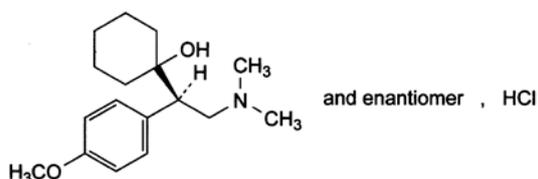
Nomenclature:

INN: Venlafaxine

Chemical names: i) (±)-1-[2-(Dimethylamino)-1-(4-methoxy phenyl)ethyl]cyclohexanol hydrochloride

ii) N,N-Dimethyl-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethylamine hydrochloride

Structure:



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

Molecular weight: 313.9

CAS No: 99300-78-4

Physical form: White or almost white powder

Solubility: Freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone.

Stereochemistry: It displays polymorphism. It is a racemate with two active enantiomers.

The active substance, venlafaxine hydrochloride, is the subject of a European Pharmacopoeia (EP) monograph.

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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal or biological origin, and therefore comply with the TSE requirements.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed into double polythene bags as the primary container. The polythene bags are then packed into triple laminated high barrier bags. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polythene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 2 years.

II.3 MEDICINAL PRODUCT

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Comparative dissolution and impurity data for each strength tablet were provided for the generic tablets and appropriate comparator products (including originator products) sourced from various markets. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of Opadry 03B23319 Orange which makes up the tablet coating, and one of its constituents, sunset yellow FCF lake (E110). These both comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. 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.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 48 months has been set, which is satisfactory. There are no special precautions for storage.

Bioequivalence Study

A single bioequivalence study was submitted comparing the test product, Venlafaxine 37.5mg tablets, to the reference product, Efexor 37.5mg Tablets (Wyeth Laboratories, UK).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Venlafaxine 37.5 mg Tablets is a generic medicinal product of Efexor 37.5 mg Tablets appears justified. As the test products, Venlafaxine 37.5 mg and 75 mg Tablets, 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 37.5 mg strength were extrapolated to the 75 mg strength tablets.

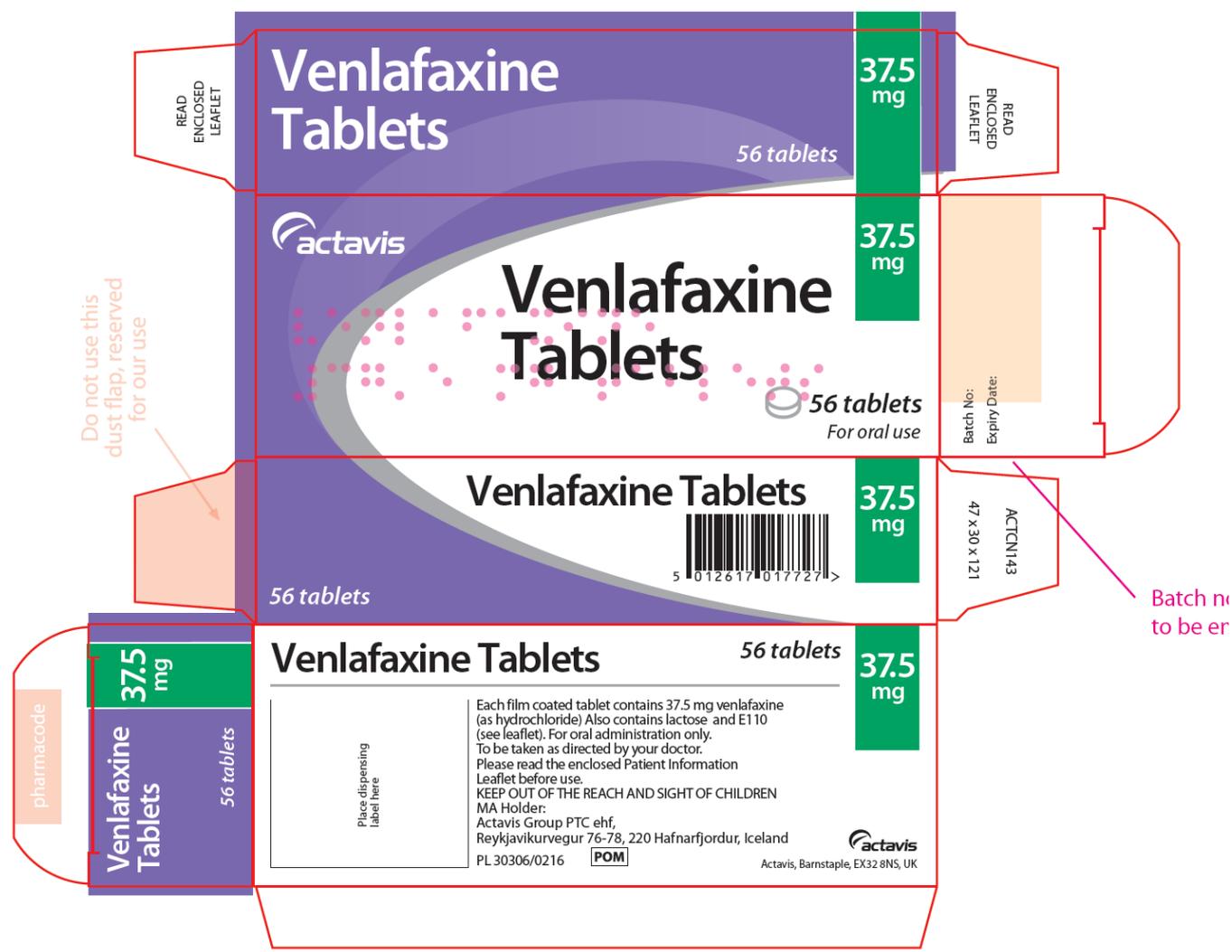
All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It was, therefore, recommended that Marketing Authorisations be granted.

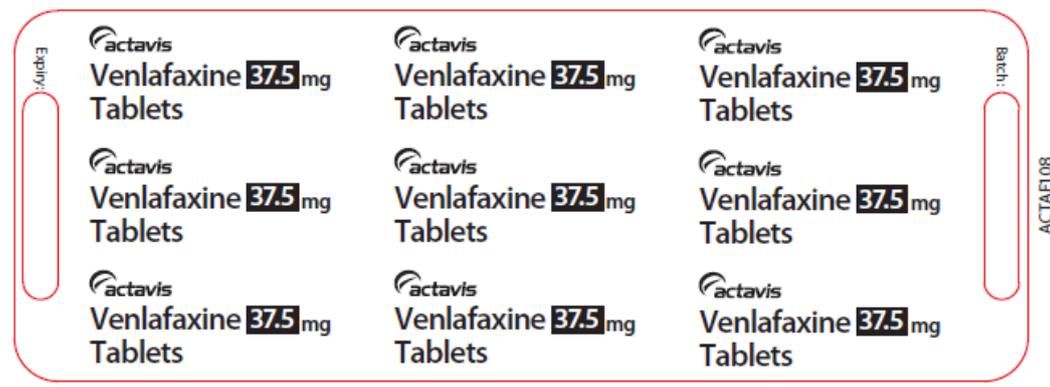
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

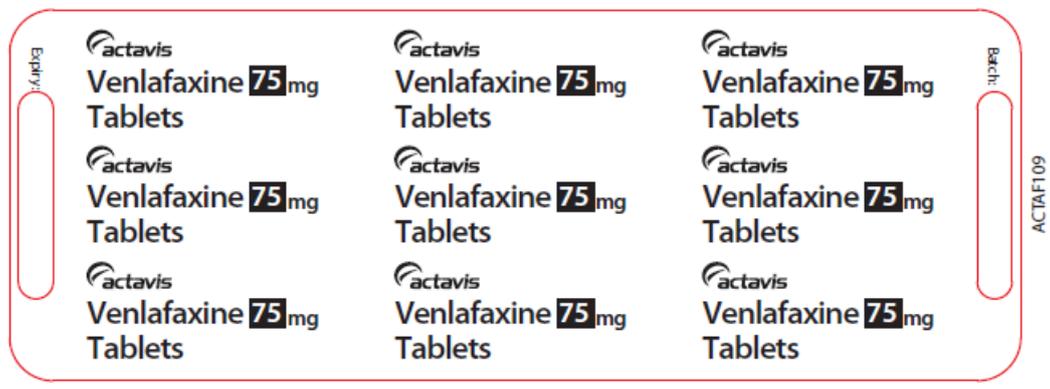
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

Venlafaxine 37.5 mg Tablets:





Venlafaxine 75 mg Tablets:



III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of venlafaxine hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology

Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for generic substitution with products that are already marketed, no increase in environmental exposure to venlafaxine hydrochloride is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for Venlafaxine 37.5 mg and 75 mg Tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of venlafaxine hydrochloride is well-known.

In accordance with the regulatory requirements for a modified release generic product claiming to be bioequivalent to a reference product (CPMP/EWP/QWP/280/96. Corr), the applicant submitted a bioequivalence study. The results of the bioequivalence study are discussed in Section IV.2, Pharmacokinetics.

With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for these applications.

IV.2 Pharmacokinetics

The pharmacokinetics properties of venlafaxine are well described. It is well absorbed (>92%) and undergoes extensive first-pass metabolism. Bioavailability is unaffected by food. Considerable intrasubject variability is seen. Mean peak plasma concentrations of venlafaxine range from approximately 33 to 172ng/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 (ODV) is the major active metabolite of venlafaxine. The mean disposition half-life of venlafaxine and ODV is approximately 5 and 11 hours, respectively. Mean peak ODV plasma concentrations range from approximately 61 to 325ng/ml and are reached in approximately 4.3 hours. Venlafaxine and ODV are 27% and 30% bound to plasma proteins respectively. ODV, other minor venlafaxine metabolites, and non-metabolised venlafaxine are excreted primarily through the kidneys.

Pharmacokinetics - Bioequivalence study

The applicant presented a single bioequivalence study comparing the test product, Venlafaxine 37.5 mg Tablets, to the reference product, Efexor 37.5 mg Tablets (Wyeth Laboratories, UK). Satisfactory Certificates of Analysis for the test and reference products were provided. The study was conducted in accordance with current standards of Good Clinical Practice.

The design was a randomised, open, two-treatment, two-period, two-way crossover, single dose bioequivalence study, performed in 40 healthy adult human volunteers (plus two alternates) under fasting conditions. Single oral 37.5mg doses were separated by an adequate washout period of 14 days. Serum drug levels were followed for 48 hours following dosing. An adequate statistical plan was provided. Both Log-transformed and non-transformed data for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} were analysed by ANOVA.

Bio-study outcome and results:

Of the 42 (40 + 2 alternates) enrolled, only 29 evaluable subjects completed the clinical part of the study, due mainly to the occurrence of nausea and vomiting. Therefore it was decided to dose 11 additional subjects with 5 further alternates in order to reach the originally planned sample size of 40. This is satisfactory.

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

Pharmacokinetic results (mean + (SD)) for a randomised single dose 2-way crossover study between the test and reference products. Log transformed. ANOVA. n=40 healthy subjects, dosed fasted; t=48 hours. Wash-out period: 2 weeks

Test parameter	Test product (geometric means)	Reference product (geometric means)	Ratio (%) Test/reference x 100	90% Confidence intervals (%)
Venlafaxine				
AUC_{0-t} (ng.h/ml)	491.39 (479.86)	472.67 (482.03)	103.8	98.4 -109.5
$AUC_{0-\infty}$ (ng.h/ml)	509.62 (520.77)	491.94 (532.73)	103.8	98.5 – 109.4
C_{max} (ng/ml)	61.18 (30.89)	57.58 (25.83)	104.3	98.1 – 111.0
T_{max} (h)*	1.87 (0.83)	1.74 (0.83)	-	-
$T_{1/2}$	5.11 (2.48)	5.29 (2.66)	-	-
O-desmethylvenlafaxine				
AUC_{0-t} (ng.h/ml)	1499.1 (370.31)	1513.2 (391.19)	99.2	95.9 – 102.6
$AUC_{0-\infty}$ (ng.h/ml)	1573.5 (394.26)	1586.3 (417.93)	99.4	96.1 – 102.8
C_{max} (ng/ml)	87.23 (26.34)	87.55 (26.86)	99.5	96.7 – 102.4
T_{max} (h)*	3.93 (1.87)	3.57 (1.92)	-	-
$T_{1/2}$	10.24 (2.71)	10.16 (2.43)	-	-

* median values - non-parametric confidence intervals (Hauschke et al.)

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%, such that the test and reference products may be considered bioequivalent after a single dose under fasted conditions.

As these applications for both strengths are supported by a single bio-study on the 37.5 mg strength, it is necessary to consider the linearity of kinetics over the therapeutic range i.e. up to the maximum recommended dose of 375 mg per day. Venlafaxine is virtually completely absorbed at therapeutic doses from either tablets or oral solution. Given that both strengths are based on a proportional formulation, that similar dissolution profiles occur for the both strengths and that it has been established that kinetics of venlafaxine and the active metabolite are linear up to 450mg, it is acceptable that a bioequivalence study has not been performed on the 75 mg tablets.

Overall conclusions on pharmacokinetics

The 90% confidence intervals for the test/reference lie within the accepted 80.0%-125.0% bioequivalence range for both venlafaxine and its major metabolite (O-desmethylvenlafaxine). Bioequivalence of the test product to the reference formulation has, therefore, been satisfactorily demonstrated in accordance with CHMP criteria.

The multiple dose waiver criteria are met and hence the single study on the 37.5 mg strength is accepted as demonstrating bioequivalence for the 75 mg strength product.

IV.3 Pharmacodynamics

Venlafaxine is a structurally novel antidepressant which is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is a racemate with two active enantiomers.

No new data submitted. The pharmacodynamics properties 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, O-desmethylvenlafaxine (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.

IV.4 Clinical Efficacy

The efficacy is reviewed in the clinical overview. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

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

IV.5 Clinical Safety

Safety is reviewed in the clinical overview. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

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

IV.6 Risk Management Plan

Suitable justification has been provided for not submitting a Risk Management Plan for these applications that were received prior to 21 July 2012, the date from which pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. As the safety profile of the active substance is well-established, a Risk Minimisation Plan is not considered necessary. Routine Pharmacovigilance activities in accordance with EU regulations are considered sufficient.

IV.7 Discussion of the clinical aspects

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and bioequivalence of the 37.5 mg strength test and reference products was shown with 90% Confidence Intervals within general acceptance limits. The conditions, as detailed in CPMP/EWP/QWP/1401/98, for a single bioequivalence study to cover multiple strengths of a product have been met, so the results and conclusions of this bioequivalence study were extrapolated to the 75 mg strength tablets.

Sufficient clinical information has been submitted to support these applications. When used as indicated, venlafaxine has a favourable benefit-to-risk ratio. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.

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. The language used for the purpose of user testing the pack leaflet was English.

The results show that 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 Venlafaxine 37.5 mg and 75 mg 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. As the pharmacokinetics, pharmacodynamics and toxicology of venlafaxine hydrochloride are well-known, no additional data were required.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Venlafaxine 37.5 mg tablets, and the reference product Efexor 37.5 mg Tablets (Wyeth Laboratories, UK). As the test products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), and the pharmacokinetics of venlafaxine are linear over the proposed dose range, the results and conclusions of the bioequivalence study on the 37.5 mg strength were extrapolated to the 75 mg tablet strength. Thus, no separate bioequivalence studies were necessary for the 75 mg tablet strength.

SAFETY

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of venlafaxine hydrochloride is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and the valid extrapolation of its results and conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with venlafaxine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

RECOMMENDATION

The grant of Marketing Authorisations is recommended.

VENLAFAXINE 37.5MG TABLETS
VENLAFAXINE 75 MG TABLETS
(venlafaxine hydrochloride)

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Marketing Authorisation applications (PL 08608/0075 and PL 08608/0077) on 14 December 2004.
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 05 October 2005.
- 3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 07 December 2005, and subsequently 05 December 2007.
- 4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 22 March 2006 and 13 March 2008 respectively.
- 5 Upon review of responses, the MHRA requested further information relating to the quality sections on 04 April 2008 and further information relating to the clinical sections on 14 April 2008.
- 6 The applicant responded to the MHRA's request, providing further information for the quality and clinical sections on 07 May 2008.
- 7 The applications were determined on 17 September 2008.

VENLAFAXINE 37.5 MG TABLETS
VENLAFAXINE 75 MG TABLETS
(venlafaxine hydrochloride)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
05 March 2015	Type IB	To correct section 4.2 (Posology and administration) of the SmPC (remove incorrect reference to capsules).	Approved 23 March 2015.

Annex 1

Our Reference: PL 30306/0216 - 0015
Product: PL 30306/0216 ACTAVIS GROUP PTC Venlafaxine
Tablets 37.5 mg
Marketing Authorisation Holder: ACTAVIS GROUP PTC EHF
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 correct section 4.2 (Posology and administration) of the SmPC (remove incorrect reference to capsules).

Linked / Related Variation(s) or Case(s):

The Assessment Report refers to the Collection ID 161638 and covers the following submissions PL 30306/0218 – 0015.

Supporting Evidence

Revised SmPC fragments have been provided.

Evaluation

Revised SmPC fragments have been provided.

Conclusion

The amended SmPC sections have been provided and are acceptable.

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

Decision – Approved on 23 March 2015