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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Venlafex SR 37.5mg, 75mg & 150mg Prolonged-release capsule, hard
VENLAFAXINE HYDROCHLORIDE
PA 1347/36/1-3

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Venlafex SR 37.5mg, 75mg & 150mg Prolonged-release capsule, hard, from Niche Generics Limited for the following indications:

- Treatment of major depressive episodes.
- For prevention of recurrence of major depressive episodes.

This application for Venlafex SR 37.5mg, 75mg & 150mg Prolonged-release Capsules was submitted as a New National generic application in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/

Name of the product:	Venlafex 37.5 mg, 75 mg, 150 mg prolonged release capsules
Name(s) of the active substance(s) (INN)	Venlafaxine hydrochloride
Pharmacotherapeutic classification (ATC code)	N06AX16
Pharmaceutical form and strength(s)	Hard Capsules, 37.5mg, 75 mg, 150 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA 1347/36/1-3
Marketing Authorisation Holder	Krka, d.d. Novo mesto

II QUALITY ASPECTS

II.1. Introduction

This application is for Venlafex 37.5 mg, 75 mg, 150 mg prolonged release capsules.

II.2 Drug substance

The active substance is Venlafaxine hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Brief description of the dosage form

Opaque, prolonged release, hard gelatine capsules (body: white, cap: brownish-rose) containing white to off-white pellets.

Composition of the medicinal product

Each prolonged release capsule, hard, contains 37.5 mg venlafaxine (as 42.43 mg venlafaxine hydrochloride).

Excipient:

	37.5 mg capsule
sucrose	32.5 mg

For a full list of excipients, see section 6.1.

Capsule contents:
Talc
Dibutyl sebacate
Povidone K 30
Hydroxypropylcellulose
Ethylcellulose
Sugarspheres (saccharose, maize starch)

Capsule shell (37.5 mg):
Body:
Gelatine
Titanium dioxide (E171)
Cap:
Red iron oxide (E172)
Titanium dioxide (E171)
Gelatine

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for hard capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as blister in a carton.

Evidence has been provided that the blister material complies with legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years when stored without any special storage requirements.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Venlafex Capsules.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for more than 10 years. No new preclinical data have been submitted as preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

IV CLINICAL ASPECTS

IV.1 Introduction

Venlafaxine is a well known active substance with established efficacy and tolerability.

This medicinal product is the same as Efexor XL on the European market. The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Efexor XL marketed by Wyeth Pharmaceuticals.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product.

Based on the pharmacokinetic parameters of the active substance, the reference tablet and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
At least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is approximately 45%. After administration of Effexine SR, peak plasma concentrations of venlafaxine and ODV are achieved within 6.0±1.5 and 8.8±2.2 hours, respectively. The rate of absorption of venlafaxine from Effexine SR is slower than the rate of elimination. The elimination half-life of the prolonged release capsules is 15 ± 6 hours and is absorption rate limited.

Distribution
Venlafaxine and O-desmethylvenlafaxine are 27% and 30% are bound to plasma proteins, respectively.

Metabolism
Venlafaxine undergoes extensive first-pass metabolism in the liver, primarily by CYP2D6 primarily, to the major metabolite, ODV. Venlafaxine is also metabolized to N-desmethylvenlafaxine catalysed by CYP3A3 and CYP3A4, and to other minor metabolites. In CYP2D6 poor metabolisers, 2-3 times higher exposure of venlafaxine and 2-3 times lower exposure of the active metabolite ODV is achieved.

Elimination
Venlafaxine is eliminated mainly through metabolism. Venlafaxine plasma clearance is 1.3 L/h/kg, and for the active metabolite ODV it is 0.4 L/h/kg. Due to its long absorption half-life, the apparent elimination half-life of Effexine SR is 15 h and thus longer than its true elimination half-life of 5 h (ODV 11 h).

Venlafaxine and its metabolites are excreted predominantly through the kidneys. Approximately 87% of a venlafaxine dose is recovered from the urine within 48 hours as either unchanged venlafaxine, unconjugated or conjugated ODV, or other minor metabolites.

Special patients groups
Subject age and sex do not significantly affect the pharmacokinetics of venlafaxine. No accumulation of venlafaxine or ODV has been observed during chronic administration in healthy subjects.

The half lives of venlafaxine and its active metabolite O-desmethylvenlafaxine (ODV) are increased in patients with renal and hepatic impairment. A clinical study demonstrated that in hepatically impaired patients the mean plasma half-life of venlafaxine is approximately doubled (see Section 4.2)

Administration of Effexine SR with food has no effect on the absorption of venlafaxine or on the subsequent formation of ODV.

IV.3 Pharmacodynamics

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

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, ODV, are potent inhibitors of serotonin and noradrenaline reuptake. Venlafaxine also weakly inhibits dopamine uptake. Studies in animals show that tricyclic antidepressants may reduce the responsiveness of β-adrenergic receptors following chronic administration. In contrast, venlafaxine and ODV 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.

Venlafaxine has virtually no affinity for rat brain muscarinic cholinergic, H_1-histaminergic or α_1-adrenergic receptors *in vitro*. Pharmacological activity at these receptors may be related to various undesirableeffects seen with other antidepressant antidepressant medicinal products, such as anticholinergic, sedative and cardiovascular undesirable effects.

Venlafaxine does not possess monoamine oxidase (MAO) inhibitor activity.
In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-d-aspartic acid (NMDA) receptors. It has no significant central nervous system (CNS) stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

IV.4 Clinical Efficacy

The clinical efficacy of venlafaxine is well established.

IV.5 Clinical Safety

The clinical efficacy of venlafaxine is well established. A Risk Management Plan is not required in line with the known safety profile of the active substance.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance system, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

The schedule for Periodic Safety Update Reports (PSUR) submission has been addressed in line with this being a generic product. As atorvastatin is a well-established product with a known safety-profile, a 3-year-cycle for PSUR submission has been agreed.

V OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation

Venlafex SR 37.5mg, 75mg & 150mg Prolonged-release Capsules are a generic form of Efexor XL hard prolonged release capsules.

Venlafaxine is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

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

The IMB, on the basis of the data submitted considered that Venlafex SR 37.5mg, 75mg & 150mg Prolonged-release Capsules, hard, demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.