CBG MEB

Public Assessment Report

Scientific discussion

Venlafaxin SUN 37.5 mg, 75 mg and 150 mg prolonged-release tablets

(venlafaxine hydrochloride)

NL/H/3948/001-003/DC

Date: 6 January 2016

This module reflects the scientific discussion for the approval of Venlafaxin SUN 37.5 mg, 75 mg and 150 mg prolonged-release tablets. The procedure was finalised on 6 October 2010 with Germany as RMS (DE/H/2409/001-003/DC). The current RMS is the Netherlands (NL/H/3948/001-003/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Venlafaxin SUN 37.5 mg, 75 mg and 150 mg prolonged-release tablets from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for:

- treatment of major depressive episodes
- prevention of recurrence of major depressive episodes
- treatment of generalised anxiety disorder
- treatment of social anxiety disorder
- treatment of panic disorder, with or without agoraphobia.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Efexor XL 37.5 mg, 75 mg and 150 mg, controlled release capsules by Wyeth, registered since 5 August 1997.

The RMS of the initial procedure was Germany, and the concerned member states (CMS) were Spain, The Netherlands and the United Kingdom. The role of RMS was transferred to the Netherlands on 22 September 2016.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

- Venlafaxin SUN 37.5 mg is a round, pink and white coloured biconvex bilayer coated prolonged-release tablet imprinted with “760” with black ink on one side and plain on the other side. Each prolonged-release tablet contains 37.5 mg of venlafaxine (as venlafaxine hydrochloride).
- Venlafaxin SUN 75 mg is a round, pink and white coloured biconvex bilayer coated prolonged-release tablet imprinted with “759” with black ink on one side and plain on the other side. Each prolonged-release tablet contains 75 mg of venlafaxine (as venlafaxine hydrochloride).
- Venlafaxin SUN 150 mg is an oval, pink and with coloured biconvex bilayer coated prolonged-release tablet imprinted with “758” with black ink on one side and plain on the other side. Each prolonged-release tablet contains 150 mg of venlafaxine (as venlafaxine hydrochloride).

The prolonged-release tablets are packed in blisters consisting of an OPA/Aluminium/PVC film and Paper/PET/Aluminium/Peelable lidding foil with heat seal lacquer or HDPE tablet containers along with silica gel canister closed with child resistant closure.

The excipients are for the tablet core:
tablet core (sustained release layer) – methyl hydroxypropyl cellulose, povidone K30, lactose monohydrate, methacrylic acid-ethyl arylate co-polymer (1:1), talc and magnesium stearate
tablet core (openable layer) – silicified microcrystalline cellulose, crospovidone (Type A), colloidal anhydrous silica, sodium lauryl sulphate, allura red aluminium lake (E129), talc and magnesium stearate.
coating – ethylcellulose aqueous dispersion, mannitol, povidone K30, dibutyl sebacate, triethyl citrate, polysorbate 20 and opadry II 85F19250 clear (talc, macrogol 3350, polysorabate 80 and polyvinyl alcohol).
printing ink – shellac, black iron oxide (E172) and propylene glycol.

II.2 Drug Substance

The active substance venlafaxine hydrochloride is described in the current European Pharmacopoeia (Ph Eur). The quality of venlafaxine hydrochloride is controlled in compliance with the corresponding monograph of the European Pharmacopoeia. The suitability of the monograph to test the drug substance has been verified by EDQM.
Due to updated stability data, the proposed re-test period of five years for the active substance can be accepted.

II.3 Medicinal Product

The ingredients and the manufacturing process of the drug product are considered to be suitable to produce a pharmaceutical product of appropriate quality. Relevant quality characteristics of the drug substance and the drug product (release and shelf-life) are specified. The proposed limits are accepted. Descriptions of the analytical methods used to analyse the drug substance and the drug product are adequate, the validation results are plausible.
On the basis of the stability data and taking into account the possibility of extrapolation described in the Guideline on Stability Testing: Stability Testing of Active Substances and Related Finished Products (CPMP/QWP/122/02 rev 1 corr), a shelf-life of 24 months is accepted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Venlafaxin SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Venlafaxin SUN is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Efexor XL, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Venlafaxine hydrochloride is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted 5 bioequivalence studies, single-dose (fasting and fed condition on lower and higher strengths) and steady-state studies on higher strengths.

IV.2 Pharmacokinetics

The applicant submitted 5 bioequivalence studies including single-dose (fasting and fed condition on lower and higher strengths) and steady-state studies on higher strengths to confirm the bioequivalence of the applicant´s formulation to the brand leader. Apart from that, in-vitro dissolution data of Venlafaxin SUN and Efexor XL in three different media were provided.

Biowaiver
The results of the bioequivalence study with the 37.5 mg and 150 mg strengths are also valid for 75 mg tablets since, according to the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98), the selection of the strength for bioequivalence study is necessary for products with several strengths when all of the following conditions hold:

- The qualitative composition of all strengths are same;
- The ratio between the active substance and the excipients is the same;
- The dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study;
- Venlafaxine shows linear-pharmacokinetics up to the dose range of 75 to 450 mg/day.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Venlafaxin SUN 37.5 mg, 75 mg and 150 mg prolonged-release tablets is considered bioequivalent with Efexor XL 37.5 mg, 75 mg and 150 mg, controlled release capsules.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Efexor XL. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Venlafaxin SUN 37.5 mg, 75 mg and 150 mg prolonged-release tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Efexor XL 37.5 mg, 75 mg and 150 mg, controlled release capsules. Efexor is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Venlafaxin SUN with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 6 October 2010.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Changes in imprints, bossing or other markings; transfer of production to Opacode-s-1-17823	DE/H/2409/ 1-3/IA/001	IA	10-10-2012	09-11-2012	Approved	N
Changes in specification method of an excipient from in-house to USP-NF	DE/H/2409/ 1-3/IB/002	IB	22-10-2012	04-12-2012	Approved	N
New change of packager and switch in blister use	DE/H/2409/ 1-3/IA/004	IA	27-03-2013	26-04-2013	Approved	N
Replace CEP with a declaration of the manufacturer and supplier	DE/H/2409/ 1-3/IA/005	IA	08-04-2013	07-05-2013	Approved	N
Downscaling of batch size	DE/H/2409/ 1-3/IB/006	IB	03-05-2013	25-06-2013	Approved	N
Replacement of DDPS with PSMF as well as to change the QPPV	DE/H/***/IA/ /564/G	IA/G	27-11-2013	19-12-2013	Approved	N
Updated CEP	DE/H/2409/ 1-3/IA/008	IA	23-05-2014	18-06-2014	Approved	N