COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Venlafaxine HCl Sandoz XR 225 mg, hard prolonged-release capsules

(venlafaxine hydrochloride)

NL License RVG: 120095

Date: 28 August 2019

This module reflects the scientific discussion for the approval of Venlafaxine HCl Sandoz prolonged-release tablets, hard. The procedure was finalised on 13 August 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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 Medicines Evaluation Board (MEB) has granted a marketing authorisation for Venlafaxine HCl Sandoz XR 225 mg, hard prolonged-release capsules, hard from Sandoz B.V.

The product is indicated for:

- Treatment of major depressive episodes
- For 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 national procedure concerns a generic application claiming essential similarity with the innovator product Efexor XR 150 mg prolonged-release capsules, hard by Pfizer BV. Efexor is registered through a mutual recognition procedure (SE/H/0936/003/MR) in the Netherlands since 12 July 2006.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Venlafaxine HCl Sandoz XR 225 mg is a pink opaque/pink opaque, hard gelatin capsules having a thick and thin radial circular band on the body in blue ink and a thick and thin radial circular band on the cap in blue ink. The capsule is filled with 18 white to off-white, round, biconvex, film coated mini tablets of 12.5 mg each. The capsules contain as active substance 225 mg of venlafaxine, as 254.7 mg of venlafaxine hydrochloride.

The hard capsules are packed in aluminium foil and unprinted OPA/Aluminium/PVC foil or aluminium foil and white opaque PVC/Aclar film or aluminium foil and white opaque PVC/PVdC film.

The excipients are:
Capsule content - microcrystalline cellulose (E460), povidone (K-90 D), talc, colloidal anhydrous silica, magnesium stearate, ethylcellulose, and copovidone
Capsule shell - carmoisine (E122), titanium dioxide (E171), gelatin, purified water
Capsule printing ink - shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution and indigo carmine (E132)

II.2 Drug Substance

The active substance is venlafaxine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white to almost white powder, and is freely soluble in water. Venlafaxine has one chiral centre. The drug substance is a racemate. Polymorphic form B is manufactured.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It meets the requirements of the monograph in the Ph.Eur. and includes additional tests for solid phase identification, particle size distribution, microbial limits and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients justified. Venlafaxine hydrochloride prolonged-release capsules are developed by compressing the drug and selected diluents into mini-tablets and then coating these mini-tablets with a release controlling polymer(s). The manufacturing process development has been adequately described and critical aspects identified.

Three bioequivalence studies have been performed using 150 mg test and reference products. The dissolution profiles in support of a biowaiver of strength for the 225 mg product are similar to the bioequivalence batch of 150 mg.
The dissolution profiles were studied in water (all products) and 0.1 N HCl, acetate buffer (pH 4.5) and Phosphate buffer (pH 6.8). The comparative dissolution profiles for biowaiver of

strength for the 225 mg at the four media show also similarity to the test batch used for the bioequivalence studies. F_2 values were calculated and are between 50 and 100.

Manufacturing process

The manufacture of the drug products comprises of manufacture of core mini tablets of 12.5 mg and its coating with release controlling polymers. The coated tablets are then filled in capsules. Appropriate in-process controls are applied throughout the manufacture of tablets to ensure the acceptable physical characteristics, including the specification of the film-coated mini-tablets (dissolution limit acceptable). Critical steps have been identified. The manufacturing of the drug product has been adequately described.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the requirements for their respective Ph.Eur. monographs. For the empty hard gelatine capsules acceptable in-house specifications are used. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average filled content, uniformity of dosage units, loss on drying, assay of venlafaxine, dissolution, related substances, residual solvents, XRD and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from pilot and commercial scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Three pilot scaled batches were tested for 36 months long term (25°C/60% RH) and 6 months accelerated (40°C/75% RH). None significant change is observed. On basis of the data submitted, a shelf life was granted of 36 months. A photostability study was performed. From the study it can be concluded that the product is photo stable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies

For gelatin, certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Venlafaxine HCl Sandoz XR 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 Venlafaxine HCl Sandoz XR 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 generic formulation of Efexor XR 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 MEB agrees 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 MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted a single dose fasting-, a single dose fed-, and a multiple dose study under fed conditions bioequivalence study in which the pharmacokinetic profile of the test product Venlafaxine HCl Sandoz XR 150 mg (Sandoz B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Trevilor retard 150 mg (Pfizer Pharma GmbH, Germany).

The choice of the reference product

The choice of the reference product in the bioequivalence studies has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Biowaiver

Extrapolation of the results from the bioequivalence study to the 225 mg strength is possible as the following criteria according the EMA guideline are fulfilled:

- the pharmacokinetic of venlafaxine is linear;
- the qualitative composition of the capsules is the same;
- the ratio between active substance and the excipients in all strengths of the test product is the same;
- the dissolution rate of the 150 mg biobatch of the test product *in vitro* is similar to the 225 mg strength at all tested conditions

Bioequivalence study I - Single dose study under fasting conditions

Design

An open label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects (mean age 29.2 years). Each subject received a single dose (150 mg) of one of the two venlafaxine hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of eight days.

Blood samples were collected at pre-dose and at 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 9.50, 10.00, 10.50, 11.00, 12.00, 16.00, 20.00, 24.00, 48.00 and 72.00 after administration of the products.

The design of the study is acceptable. The highest 225 mg strength would not be feasible in healthy volunteers due to tolerability reasons which could result in an earlier termination of a study. Due to the risk of dose-related adverse effects, the lowest effective dose should be maintained. The choice of the 150 mg strength is therefore considered justified. This

approach was also accepted in a scientific advice from the Medicines and Health products Regulatory Agency (MHRA).

Results

Two subjects were dropped out from the study on their own accord due to their personal reasons before check-in of period 1. Five subjects were withdrawn from the study on medical/safety grounds and on vomiting after period 1 dosing. One subject was withdrawn from the study on medical/safety grounds during period 1. One subject was withdrawn from the study on medical/safety grounds during period 1 washout. Two subjects didn't report to the clinical facility for period 2 check-in. And one subject was withdrawn from the study on medical/safety grounds and on vomiting after period-2 dosing. Therefore, 34 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of venlafaxine under fasted conditions.

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	2778.5 ± 2238	2891.7 ± 2402	127.2 ± 65	7.5 (5.00 – 11.00)
Reference	2483.4 ± 1694	2594.5 ± 1950	125.9 ± 53	6.5 (5.00 – 12.00)
***Ratio (90% CI)**	1.09 (1.04 – 1.14)	1.10 (1.05 – 1.15)	0.99 (0.95 – 1.04)	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration

**ln-transformed values*

Bioequivalence study II - Single dose study under fed conditions

Design

An open label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study was carried out under fasted conditions in 45 healthy male subjects (mean age 31.2 years). Each subject received a single dose (150 mg) of one of the two venlafaxine hydrochloride formulations. Subjects were fasted overnight for at least 10 hours prior to a high-fat high-calorie breakfast. Dosing was done 30 minutes after the start of the breakfast. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of eight days.

Blood samples were collected at pre-dose and at 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 9.50, 10.00, 10.50, 11.00, 12.00, 16.00, 20.00, 24.00, 48.00 and 72.00 after administration of the products.

The design of the study is acceptable. The highest 225 mg strength would not be feasible in healthy volunteers due to tolerability reasons which could result in an earlier termination of a study. Due to the risk of dose-related adverse effects, the lowest effective dose should be

maintained. The choice of the 150 mg strength is therefore considered justified. This approach was also accepted in a scientific advice from MHRA.

Results

One subject dropped out from the study on his own accord due to his personal reasons before check-in of period-1. One subject was withdrawn from the study on medical/safety grounds and due to vomiting at critical time as specified in the approved study protocol after period 1 dosing. One subject was found positive in breath alcohol test during period 2 check in. One subject was found positive in urine scan for drug of abuse test during period 2 check-in. One subject didn't report to the clinical facility for period 2 check-in. One subject was withdrawn from the study on medical/safety grounds and pharmacokinetic reasons due to adverse event of vomiting after period 2 dosing. Therefore 39 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of venlafaxine under fasted conditions.

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	26034 ± 1982	2701 ± 2090	122.7 ± 57	9.0 (5.00 – 48)
Reference	2499.8 ± 1548	2554 ± 1596	127.34 ± 51	5.57 (4.00 – 12.00)
***Ratio (90% CI)**	0.94 (0.86 – 1.03)	0.94 (0.87 – 1.03)	0.93 (0.87 – 1.00)	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration

**ln-transformed values*

Bioequivalence study III – Steady state study under fed conditions

Design

An open label, balanced, randomised, two-treatment, two-sequence, two-period, multiple-dose, crossover, steady state oral bioequivalence study was carried out under fasted conditions in 44 healthy male subjects (mean age 31.2 years). One capsule of either the test product or the reference medicinal product through randomisation will be administered to each subject on each dosing day (dose 1 to dose 4) at an interval of 24 hours in each period with about 240 ml of water at ambient temperature. Subjects were fasted overnight for at least 10 hours prior to scheduled time for dosing on dosing day 1 to 3 in each period. Dosing of dose 4 in each period was done 30 minutes after the start of a high-fat high-caloric breakfast. Subjects were instructed to consume the whole high-fat high-calorie breakfast within 30 minutes of the serving after an overnight fast of at least 10 hours. There was no wash-out between the two periods.

Blood samples were collected at within 5 minutes prior to dosing of dose 2 to 4 and at 1.00, 2.00, 3.00, 4.00, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 9.50, 10.00, 10.50, 11.00,

12.00, 16.00, 20.00 and 24.00 hours (within 2 minutes) after dosing of dose 4 in each period after administration of the products.

The study design and the sampling schedule are adequate. The lack of wash-our period is acceptable since the build up time in period 2 was long enough to wash-out venlafaxine from period 1 ($t_{1/2}$ of venlafaxine from a prolonged release capsule is 15 hours).

Results

One subject withdrew his consent prior to dosing of dose 1 in period 1. Three subjects did not show steady state condition and therefore additional statistical analysis was performed excluding these subjects from the data set. Therefore 43 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD) excluding the three subjects

Treatment N=40	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**$C_{\tau,ss}$** ng/ml	**$t_{max,ss}$** h
Test	3105 ± 3284	175.4 ± 150	89.4 ± 136	7.00 (5.00 – 20.00)
Reference	3265 ± 3004	194.4 ± 135	92.2 ± 126	5.5 (3.00 – 12.00)
***Ratio (90% CI)**	0.93 (0.87 – 0.98)	0.88 (0.81 – 0.94)	0.92 (0.83 – 1.01)	--
AUC_τ	area under the plasma concentration-time curve over the dosing interval			
C_{max}	maximum plasma concentration			
$C_{\tau,ss}$	Plasma concentration at the end of the dosing interval at steady state			
$t_{max,ss}$	Time until $C_{max,ss}$ is reached			

Table 4. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD) including the three subjects

Treatment N=43	**AUC_τ** ng/ml/h	**C_{max}** ng/ml	**$C_{\tau,ss}$** ng/ml	**$t_{max,ss}$** h
Test	3269 ± 3343	185 ± 157	95 ± 135	7.0 (5.00-20.00)
Reference	3405 ± 3065	201 ± 139	98 ± 127	5.5 (3.00 – 12.00)
***Ratio (90% CI)**	0.93 (0.88 – 0.98)	0.88 (0.82 – 0.94)	0.92 (0.84 – 1.01)	--
AUC_τ	area under the plasma concentration-time curve over the dosing interval			
C_{max}	maximum plasma concentration			
$C_{\tau,ss}$	Plasma concentration at the end of the dosing interval at steady state			
$t_{max,ss}$	Time until $C_{max,ss}$ is reached			

<u>Conclusion on bioequivalence studies</u>

The 90% confidence intervals calculated for AUC_τ, $C_{\tau,ss}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Venlafaxine HCl Sandoz XR 150 mg is considered bioequivalent with Trevilor retard 150 mg. The results of the bioequivalence studies can be extrapolated to the 225 mg strength.

The MEB has been assured that the bioequivalence study has 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 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Venlafaxine HCl Sandoz XR.

Table 5. Summary table of safety concerns as approved in RMP

Important identified risks	• Withdrawal syndrome • Increased blood pressure/ Increased heart rate • Lipid effects (elevated cholesterol, elevated triglycerides and hyperlipidemias) • Hyponatremia • Convulsion • Serotonin syndrome • Suicidality • Abnormal bleeding: ecchymosis, hematomas, epistaxis, and petechiae to life-threatening haemorrhages • Interactions with other drugs: Monoamine oxidase inhibitors (MAOIs) • Severe cutaneous a reactions (SCAR) including Stevens-Johnson syndrome (SJS), Erythema multiforme (EM) and toxic epidermal necrolysis (TEN) • Mania/hypomania • SCAR including SJS, EM and TEN • Anaphylaxis • QT prolongation/ Torsade de pointes • Angle closure glaucoma
Important potential risks	• Ischemic cardiac events • Diabetes • Aggression including homicidal behaviour
Missing information	• Use in elderly patients • Use in paediatric patients • Use in pregnancy and lactation • Use in severe hepatic impairment

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Efexor XR prolonged-release capsules, hard. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has (PL) 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 test consisted of: two rounds with 10 participants each. The 15 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Venlafaxine HCl Sandoz XR 225 mg, hard prolonged-release capsules, hard has a proven chemical-pharmaceutical quality and is a generic form of Efexor XR 150 mg prolonged-release capsules, hard. Efexor XR 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.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Venlafaxine HCl Sandoz XR with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 13 August 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Case description	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Type IA: B.III.1.a.2; Type IA: B.III.1.b.3	- Updated Ph. Eur. certificate of suitability to the relevant Ph.Eur. Monograph; updated certificate from an already approved manufacturer - Updated European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/ reagent/intermediate/or excipient; updated certificate from an already approved manufacturer	-	11-3-2019	Approval	--
Type IA: B.II.d.1.d	Change in the specification parameters and/or limits of the finished product; deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	Yes	15-4-2019	Approval	--