LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Venlafaxin Liconsa / Venlafaxin 1A Farma / Venlafaxin Medical Valley (venlafaxine hydrochloride)

SE/H/564/05/DC
SE/H/581/05/DC
SE/H/582/05/DC

This module reflects the scientific discussion for the approval of Venlafaxin Liconsa Venlafaxin 1A Farma,Venlafaxin Medical Valley. The procedure was finalised on 2019-01-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Laboratorios Liconsa has applied for a marketing authorisation for Venlafaxin Liconsa, Venlafaxin 1A Farma, Venlafaxin Medical Valley, 300 mg, Prolonged-release tablet. The active substance is venlafaxine hydrochloride (which 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 other conditions such as anxiety disorders).

For approved indications, see the Summary of Product Characteristics.

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

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this medicinal product has been shown to be essentially similar and refer to a product approved based on a full application with regard to non-clinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the marketing authorisation for this line extension application of a new higher 300 mg strength (the strengths 37.5, 75, 150 and 225 mg have been approved previously), the applicant has conducted one single-dose bioequivalence study comparing venlafaxine 300 mg extended-release osmotic tablets with the reference product Vandral retard 150 mg prolonged-release hard capsules (2x150 mg) in the fed state.

IV.2 Pharmacokinetics

Pharmacokinetic properties of the active substance

Venlafaxine is extensively metabolised, primarily to the active metabolite, O-desmethylvenlafaxine (ODV). At least 92% of venlafaxine is absorbed following single oral doses of immediate-release venlafaxine. Absolute bioavailability is 40% to 45% due to presystemic metabolism. After immediate-release venlafaxine administration, the peak plasma concentrations of venlafaxine and ODV occur in 2 and 3 hours, respectively. Following the administration of venlafaxine prolonged-release capsules, peak plasma concentrations of venlafaxine and ODV are attained within 5.5 hours and 9 hours, respectively. When equal daily doses of venlafaxine are administered as either an immediate-release tablet or prolonged-release capsule, the prolonged-release capsule provides a slower rate of absorption, but the same extent of absorption compared with the immediate-release tablet.

Food does not affect the bioavailability of venlafaxine and ODV. However, in the SmPC of the originator it is recommended that venlafaxine prolonged-release capsules be taken with food, at approximately the same time each day.

Venlafaxine and ODV exhibit linear kinetics over the dose range of 75 mg to 450 mg/day.

Mean ± SD plasma half-lives of venlafaxine and ODV are 5±2 hours and 11±2 hours, respectively.

Study 0957-16

Methods

This was a single-dose, two-way crossover study conducted in 52 healthy volunteers (43 completed), comparing venlafaxine 300 mg extended-release osmotic tablets with Vandral retard 150 mg prolonged-release hard capsules (at a dose of 2x150 mg) under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of venlafaxine and the metabolite O-desmethyl venlafaxine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the

log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. Bioequivalence was based on the parent drug venlafaxine and results for the metabolite were submitted as supportive data. The study was conducted between 15th March and 12th April 2017.

Results
The results from the pharmacokinetic and statistical analysis are presented in

Table **1** below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for venlafaxine, n=43.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**5016.90±4703.85**	**5140.36±4945.42**	**238.31±152.34**	**7.500 (5.000-16.000)**
Reference	**4506.40±3964.48**	**4660.81±4217.76**	**260.77±136.97**	**5.684 (4.000-11.000)**
***Ratio (90% CI)**	**107.5 (102.20-113.12)**	**106.4 (101.10-111.94)**	**86.0 (80.69-91.71)**	**-**

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

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Bioequivalence studies in the fasted state as well as following multiple doses have not been performed with the applied strength but were performed with the previously approved 75 mg strength.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

For a prolonged- release formulation, bioequivalence should be demonstrated following single doses in the fasted as well as in the fed state and also following multiple-dose administration (unless there is no accumulation of the product). This is a line extension application for a single unit prolonged-release tablet. For the previously approved strengths (37.5, 75, 150 and 225 mg), it was agreed to perform most of the bioequivalence studies in the fed state (considering that the SmPC recommends administration with food) except for the 75 mg strength which was assessed both in the fed and in the fasted state. Thus, single dose fed studies were submitted for all strengths and in addition a single dose fasted study as well as a multiple dose study was performed for the 75 mg strength. Although the Note for guidance on

modified release oral and transdermal dosage forms (in force at the time of the previous application) recommended steady state studies to be performed with the highest strength, the use of a lower strength was agreed for tolerability reasons.

For a line extension of a 300 mg strength where the 150 mg and 225 mg strengths were approved with reference to a fasted study and a multiple dose study performed with the 75 mg strength, and considering the tolerability problems with the substance, is it not considered reasonable to request an additional fasted study or a multiple dose study with the new 300 mg strength. Provided that all quality aspects of biowaiver are fulfilled, and since the pharmacokinetics of vanlafaxine is linear in the therapeutic dose range, a single dose study in the fed state is considered sufficient since the SmPC recommends intake in the fed state.

Based on the submitted bioequivalence study, Venlafaxine 300 mg, extended-release osmotic tablets are considered bioequivalent with Vandral Retard, 2x150 mg, prolonged-release hard capsules following single-dose administration in the fed state. From a pharmacokinetic perspective a single dose study in the fed state is considered sufficient for this new strength provided that all quality aspects of biowaiver versus the 75 mg strength (for which multiple dose and single dose fasted studies are available) are fulfilled. The waiver is acceptable also from a quality perspective. Thus, bioequivalence has been adequately demonstrated.

IV.3 Pharmacodynamics

The clinical overview on pharmacodynamics is adequate

IV.4 Clinical efficacy

The clinical overview on efficacy is adequate

IV.5 Clinical safety

The general overview on clinical safety is adequate.

IV.6 Risk Management Plans

The MAH has submitted an updated 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 venlafaxin.

Table Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Aggression including homicidal behaviour • Diabetes • Ischemic Cardiac Events • Lack of efficacy associated with generic substitution (nocebo effect) • Potential medication error
Missing information	• Use in paediatric population • Use in patients with severe liver impairment • Use in pregnancy and breast-feeding • Use in elderly patients

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed. No post-authorisation efficacy studies are planned.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version Version 8 (0.8) signed 24-Oct-2018 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 PIL was spanish.

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, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid products, Venlafaxin Liconsa, Venlafaxin 1A Farma and Venlafaxin Medical Valley, is found adequate. There are no objections to approval of Venlafaxin Liconsa, Venlafaxin 1A Farma and Venlafaxin Medical Valley, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Venlafaxin Liconsa, Venlafaxin 1A Farma, Venlafaxin Medical Valley, 300 mg, Prolonged-release tablet. was positively finalised on 2019-02-11.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se