LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Venlafaxin Medical Valley
(venlafaxine hydrochloride)

SE/H/582/04/DC

This module reflects the scientific discussion for the approval of Venlafaxin Medical Valley. Please note that the marketing authorisation was first approved with the name "Durnit" and therefore this name is used throughout the document. The procedure was finalised at 2010-06-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Laboratorios LICONSA S.A has applied for a marketing authorisation for Durnit 37.5 mg prolonged release tablets strength/s. The active substance “Venlafaxine hydrochloride” is the same as in Durnit, 75 mg tablets, marketed by “Laboratorios LICONSA S.A” since 2008. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Durnit 37.5 mg prolonged-release tablets are presented in the form of prolonged-release tablets containing 42.43 mg of venlafaxine hydrochloride which corresponds to 37.5 mg of venlafaxine. The excipients are mannitol, povidone, macrogol, microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, cellulose acetate, hypromellose, lactose monohydrate, titanium dioxide and triacetin. The tablets are packed in PVC-ACLAR/Al-blister or HDPE bottle.

II.2 Drug Substance

Venlafaxine hydrochloride is a white or almost white powder which is freely soluble in water and in methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone. The structure of venlafaxine hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism, chirality and solubility is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Durnit 37.5 mg prolonged-release tablets are formulated using excipients described in the Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as polymorphism and stability.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30°C.

III. NON-CLINICAL ASPECTS

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The absolute oral bioavailability is estimated to 42 $\pm$ 15%. C_{max} is reached after approximately 2 hours (0.5-6h) and the elimination half-life is 5 hours (3-7h). The active metabolite O-desmethylvenlafaxine reaches maximal plasma concentrations after approximately 4 hours (1-8h) with a half-life of approximately 11 hours (9-13h). The interindividual variability is large. The protein binding of venlafaxine is approximately 27 % and for O-desmethylvenlafaxine approximately 30 %. Venlafaxine is metabolized via the cytochrome P-450 isoenzyme 2D6. Venlafaxine undergoes extensive first-pass metabolism to the active metabolite, O-desmethylvenlafaxine. In poor metabolisers the exposure is approximately 2-3 times higher and lower of venlafaxine and O-desmethylvenlafaxine respectively. Only 5 % (1-13%) of the dose is excreted unchanged in the urine. The metabolites are primarily excreted via the kidneys. From a radioactively labelled dose 87 % is found in the urine within 48 hours. Concomitant food intake does not affect the amount absorbed. However, a delayed T_{max} of 15-30 min is seen when the tablets are administered with food. The kinetics has been shown to be linear in the therapeutic dose range and up to 150 mg t.i.d. Klamerus KJ et al, J Clin Pharmacol. 1992 Aug; 32(8):716-24.

To support the application, the applicant has submitted two bioequivalence studies, namely VEN-BESD-03-LIC/05 and VEN-BEMD-05-LIC/05 (single and multiple doses 37.5 mg. The single dose study was performed in fed conditions only. This is considered appropriate, based on the posology of the originator. A food interaction study has been provided in a previous procedure for other strengths of the same product.

Bioequivalence was shown with respect to $AUC_{0-t,}$ $AUC_{0-\infty}$, AUC_{τ} (multiple doses studies), C_{max} and C_{min} (multiple doses studies) for venlafaxine. Within the multiple doses studies no confidence intervals for the metabolite were presented, this is justifiable based on the linear pharmacokinetics of venlafaxine within the therapeutic range and up to 150 mg t.i.d. One question was raised in the previous procedure regarding the influence of vomiting for which a satisfactory answer has been provided and included in the Day 70 Pharmacokinetic assessment report.

IV.2 Pharmacodynamics and Clinical efficacy

The clinical overview on the clinical pharmacology and efficacy is adequate.

IV.3 Clinical safety

The general overview on clinical safety is adequate.

IV.4 Discussion on the clinical aspects

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
The package leaflet is identical to the PIL for the already approved higher strengths of Durnit. The package leaflet is also in accordance with the referral procedure for the originator Efexor. Hence, no user testing is relevant in this procedure.

VI. APPROVAL

The risk/benefit ratio is considered positive and Durnit 37.5 mg prolonged release tablets strength/s is recommended for approval.

The Mutual recognition/Decentralised procedure for Durnit 37.5 mg prolonged release tablets strength/s was successfully finalised on 2010-06-17.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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