

Public Assessment Report

Scientific discussion

Venlafaxin Medical Valley (venlafaxine hydrochloride)

SE/H/582/01-03/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 on June 18th 2007. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

Licons S.A. has applied for a marketing authorisation for Durnit, 75, 150 and 225 mg prolonged release tablets, claiming essential similarity to Efexor, prolonged release capsules, 75 and 150 mg marketed in Sweden/EU by Wyeth. The product contains venlafaxine hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Effexor/Vandral Retard manufactured by Wyeth Medica Ireland.

II. QUALITY ASPECTS

II.1 Introduction

Durnit are presented in the form of prolonged release tablets containing 84.86 mg, 169.72 mg or 254.58 mg of venlafaxine hydrochloride, which corresponds to 75, 150 or 225 mg of venlafaxine, respectively. The excipients are mannitol, povidone, macrogol, microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate, cellulose acetate and Opadry Y-30-18037 (containing hypromellose, lactose monohydrate, titanium dioxide and triacetin). The prolonged release tablets are packed in two types of container: PVC-ACLAR/Al-blister and HDPE bottle.

II.2 Drug Substance

Venlafaxine hydrochloride has a monograph in the Ph Eur.

Venlafaxine hydrochloride is a white to almost white powder, which is freely soluble in water and in methanol, soluble in anhydrous ethanol and 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, 75, 150 and 225 mg prolonged release tablets are formulated using excipients described in the current 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 (EMA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as aqueous solubility, 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

III.1 Discussion on the non-clinical aspects

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

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 six bioequivalence studies, namely VEN-BESD-03-LIC/05, VEN-BEMD-05-LIC/05 (single and multiple doses 37.5 mg), VEN-BESD-02-LIC/05, VEN-BEMD-04-LIC/05 (single food interaction study and multiple doses 75 mg), VEN-BESD-06-LIC/05 (single dose 150 mg) and VEN-BESD-07-LIC/05 (single dose 225 mg). The single dose studies besides the food interaction study was performed in fed conditions only. This is considered appropriate, based on the posology of the originator.

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 within the therapeutic range and up to 150 mg t.i.d.

A few issues were raised regarding the pharmacokinetic part that was solved satisfactorily.

IV.2 Discussion on the clinical aspects

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

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed. The user testing was not optimally performed, since there were translation errors which the applicant should take into account in future applications.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence. The absence of multiple dose studies with the 150 mg and 225 mg tablet strengths is considered acceptable from a pharmacokinetic point of view since the pharmacokinetics is linear in the therapeutic dose range and these formulations are proportional to the 75 mg strength. Multiple dose studies with the two highest strengths are considered not suitable for healthy volunteers. The 75 mg strength is proportional to the 150 and 225 mg strength.

The risk/benefit ratio is considered positive and Durnit was recommended for approval.

The applicant has committed to harmonise the product information with the referral procedure of the innovator within 3 months after the scheduled harmonisation.

VI. APPROVAL

The decentralised procedure for Durnit, prolonged release tablets, 75, 150 and 225 mg was successfully finalised on 20070618.

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)