LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Citalopram Vitabalans
20 and 40 mg film-coated tablets
(citalopram hydrobromide)

SE/H/818/01-02/DC

This module reflects the scientific discussion for the approval of Citalopram Vitabalans. The procedure was finalised on 19 November 2010. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Vitabalans Oy has applied for a marketing authorisation for Citalopram Vitabalans 20 and 40 mg film-coated tablets claiming essential similarity to Cipramil 20 m and 40 mg film-coated tablets, marketed in Sweden by H. Lundbeck A/S. The product contains citalopram hydrobromide as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bioequivalence study is Cipramil 40 mg film-coated tablet from Finland.

II. QUALITY ASPECTS

II.1 Introduction

Citalopram Vitabalans is presented in the form of film-coated tablets containing 20 and 40 mg of citalopram as citalopram hydrobromide. The excipients are cellulose microcrystalline, mannitol, silica colloidal anhydrous, magnesium stearate, polydextrose, hypromellose, titanium dioxide and macrogol. The tablets are packed in PVC/PVdC-aluminium blister packs.

II.2 Drug Substance

Citalopram hydrobromide has a monograph in the Ph Eur. Citalopram hydrobromide is a white to off-white crystalline powder which is freely soluble in methanol, soluble in dichlormethane, sparingly soluble in water, ethanol and acetone and slightly soluble in isopropanol, ethyl-acetate and toluene.

The structure of citalopram hydrobromide has been adequately proven and its physico-chemical properties sufficiently described. There is no evidence of polymorphic forms. The substance is a racemic mixture. 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 and 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 4 years.

II.3 Medicinal Product

Citalopram Vitabalans film-coated tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin. The supplier of magnesium stearate has confirmed that only fatty acids of 100 % vegetable origin is used in the manufacture at the production facility in. Also during the process the material does not come into contact with any animal derived products.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

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 of 4 years with no special storage precautions when stored in PVC/PVdC/Al blister package.

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

Pharmacokinetics
The oral bioavailability of citalopram is >80% and maximum plasma concentration occurs within 4 hours of oral administration. The absorption rate and extent is not affected by concomitant food intake, and there are no restrictions with respect to food in the SPC of the originator. Citalopram shows linear pharmacokinetics in the therapeutic dose interval.

Citalopram is mainly eliminated by metabolism (85%) and the remainder (15%) is excreted via the kidneys. The half-life is about 36 h for citalopram. Most metabolic reactions are catalysed by cytochrome P450 enzymes, among others CYP2D6 and CYP2C19. The main metabolites are desmetylcitalopram and didesmetylcitalopram and they have less pharmacological effect and are not considered to contribute to the pharmacological effect of citalopram.

To support the application, the applicant has submitted one bioequivalence study (Clinical Study Report V-806) performed using the 40 mg tablet. The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted in 28 healthy volunteers under fasting conditions. Bioequivalence was demonstrated as AUC and Cmax for citalopram were within the pre-specified limits of 80-125%.

The applicant claims that bioequivalence of the other strength 20 mg could be concluded since all conditions for biowaiver of additional strength according to the Note for guidance on the investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. From a pharmacokinetic point of view, absence of studies with the additional strength is acceptable, as the pharmacokinetics of citalopram is linear within the therapeutic dose range.

The product was recommended for approval from a pharmacokinetic point of view.

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 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 Czech.
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.

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 risk/benefit ratio is considered positive and Citalopram Vitabalans 20 and 40 mg film-coated tablets are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Citalopram Vitabalans 20 and 40 mg film-coated tablets was successfully finalised on 19 November 2010.

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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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