

Public Assessment Report Scientific discussion

Bupropion Orion (bupropion hydrochloride)

SE/H/1418/01-02/DC

This module reflects the scientific discussion for the approval of Bupropion Orion. The procedure was finalised on 2015-05-21. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

The application for Bupropion Orion, 150 mg and 300 mg, modified-release tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FI and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Zyban, 150 mg, prolonged-release tablet authorised in SE since 2000, with GlaxoSmithKline AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Elontril, 150 mg, modified-release tablet and Elontril, 300 mg, modified-release tablet from DE with GlaxoSmithKline GmbH & Co. KG as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 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 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

Introduction

Absorption: The absolute oral bioavailability of bupropion is not known, but urinary excretion data show that at least 87% of the dose is absorbed. Following an oral dose of bupropion modified release tablets (XL) maximal plasma concentrations occur at approximately 5 hours. With bupropion prolonged-release tablets (SR) maximal plasma concentrations are reached after 2.5-3 hours.

The pharmacokinetics of bupropion modified release tablets is not significantly affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator Voxra/Elontril.

Linearity: The pharmacokinetics of bupropion is linear within the dose range 50-200 mg following single dose and 300-450 mg/day following repeated doses.

Elimination: The terminal half-life is approximately 20 hours.

Submitted BE –studies

To support the application, the applicant has submitted 6 bioequivalence studies:

- BUPR-1K-507-12: Single-dose study in the fasted state with the 300 mg strength
- BUPR-1K-508-12: Single-dose study in the fed state with the 300 mg strength
- BUPR-1K-510-12: Multiple-dose study in the fasted state with the 300 mg strength
- 124-11: Single-dose study in the fasted state with the 150 mg strength.
- 182-11: Single-dose study in the fed state with the 150 mg strength
- 220-13: Multiple-dose study in the fasted state with the 150 mg strength

In all six studies, plasma concentrations of bupropion were determined with a validated achiral LC/MS/MS method. The use of an achiral analytical method is acceptable since there is no pronounced difference in pharmacodynamics between the enantiomers.

Study BUPR-1K-507-12 was a single-dose, two-way crossover study conducted in 42 healthy volunteers, comparing Bupropion hydrochloride, 300 mg, modified release tablets with Elontril® (Bupropionhydrochlorid), 300 mg, modified release tablets, by GlaxoSmithKline GmbH & Co. Kg under fasting conditions.. Blood samples were collected pre-dose and up to

120 hours post-dose. The study design is considered acceptable. For AUC_{0-t} , AUC_{inf} 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%.

Study BUPR-1K-508-12 was a single-dose, two-way crossover study conducted in 44 healthy volunteers, comparing Bupropion hydrochloride, 300 mg, modified release tablets with Elontril® (Bupropionhydrochlorid), 300 mg, modified release tablets, by GlaxoSmithKline GmbH & Co. Kg under fed conditions.. Blood samples were collected pre-dose and up to 120 hours post-dose. The study design is considered acceptable. For AUC_{0-t} , AUC_{inf} 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%.

Study BUPR-1K-510-12 was a multiple-dose, two-way crossover study conducted in 44 healthy volunteers, comparing Bupropion hydrochloride, 300 mg, modified release tablets with Elontril® (Bupropionhydrochlorid), 300 mg, modified release tablets, by GlaxoSmithKline GmbH & Co. Kg under fasting conditions.. Blood samples were collected pre-dose and up to 24 hours post-dose following dose number 8 and also pre-dose of dose 1-7. The study design is considered acceptable and steady-state has been reached. For $AUC_{0-\tau}$, C_{min} 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%.

Study 124-11 was a single-dose, two-way crossover study conducted in 50 healthy volunteers, comparing Bupropion Hydrochloride, 150 mg, modified release tablets with Elontril® (Bupropionhydrochlorid), 150 mg, modified release tablets, by GlaxoSmithKline GmbH & Co., Germany under fasting conditions.. Blood samples were collected pre-dose and up to 120 hours post-dose. The study design is considered acceptable. For AUC_{0-t} , AUC_{inf} 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%.

Study 182-11 was a single-dose, two-way crossover study conducted in 52 healthy volunteers, comparing Bupropion hydrochloride, 150 mg, modified release tablets with Elontril® (Bupropionhydrochlorid), 150 mg, modified release tablets, by GlaxoSmithKline GmbH & Co. Kg under fed conditions.. Blood samples were collected pre-dose and up to 120 hours post-dose. The study design is considered acceptable. For AUC_{0-t} , AUC_{inf} 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%.

Study 220-13 was a multiple-dose, two-way crossover study conducted in 56 healthy volunteers, comparing Bupropion hydrochloride, 150 mg, modified release tablets with Elontril® (Bupropionhydrochlorid), 150 mg, modified release tablets, by GlaxoSmithKline GmbH & Co. Kg under fasting conditions.. Blood samples were collected pre-dose and up to 24 hours post-dose following dose number 8 and also pre-dose of dose 1, 6 and 7. The study design is considered acceptable and steady-state has been reached. For $AUC_{0-\tau}$, C_{min} 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%.

Pharmacokinetic conclusion

A full study package (single-dose study in the fed and in the fasted state and a multiple-dose study) has been submitted for both applied strengths. A biowaiver is therefore not applicable. The study package is sufficient for approval of both strengths.

Bioequivalence has been sufficiently demonstrated for both strengths.

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.

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 bupropion.

Safety specification

Summary table of safety concerns as approved in RMP

<i>Important identified risks</i>	• <i>Seizures</i> • <i>Hypersensitivity</i> • <i>hypertension</i>
<i>Important potential risks</i>	• <i>Interactions</i> • <i>Suicide/Suicidal thoughts or clinical worsening</i> • <i>Arrhythmias and conduction disorders</i>
<i>Missing information</i>	• -

Pharmacovigilance Plan

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

Risk minimisation measures

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

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Voxra, NL/H/786/01-02/DC (contents) and Venlafaxin Orion, DE/H/1420/01-03/DC (layout). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Bupropion Orion, 150 mg and 300 mg, modified-release tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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 Bupropion Orion, 150 mg and 300 mg, modified-release tablet was positively finalised on 2015-05-21.

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)