COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bupropion HCl 150 mg Focus Care, modified-release tablets (bupropion hydrochloride)

NL License RVG: 127105

Date: 22 February 2023

This module reflects the scientific discussion for the approval of Bupropion HCl 150 mg Focus Care, modified-release tablets. The procedure was finalised on 6 December 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Bupropion HCl 150 mg Focus Care, modified-release tablets, from Focus Care Pharmaceuticals B.V.

The product is indicated for treatment of major depressive episodes.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, essential similarity is proven between the new product and the innovator product Elontril 150 mg modified-release tablets (NL/H/0786/001, RVG 33670), registered since 10 January 2007 by GlaxoSmithKline B.V. (The Netherlands).

II. QUALITY ASPECTS

II.1 Introduction

Bupropion HCl 150 mg Focus Care is an off-white to light yellow, round, biconvex film-coated tablet. Each modified-release tablet contains as active substance 150 mg bupropion hydrochloride.

The excipients are:
Tablet core – hydroxypropyl cellulose (E463), concentrated hydrochloric acid (E507), siliconized microcrystalline cellulose, stearic acid 50 (E570) and magnesium stearate.
Tablet coating – Opadry white: ethyl cellulose (E462), hydroxypropyl cellulose (E463), titanium dioxide (E171), triethyl citrate (E1505), methacrylic acid - ethyl acrylate copolymer 1:1 and talc (E553b).

The tablets are packed in high-density polyethylene (HDPE) containers, with a desiccant, covered by a child-resistant polypropylene cap with an induction film membrane.

II.2 Drug Substance

The active substance is bupropion hydrochloride, an established active substance described in the United States Pharmacopoeia (USP). It is freely soluble in methanol, soluble in water and ethanol, very slightly soluble in acetone. The active substance does not exhibit polymorphism and there is one asymmetrical carbon atom. The active substance is used as a racemic mixture.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File

(EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Bupropion hydrochloride is manufactured in two synthetic steps followed by salt formation and purification. The manufacturing process has been described in sufficient detail. No class-I solvents or heavy metal catalysts are used in the synthesis. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and has been established based on the ASMF. In-house methods were adequately described and validated and the absence of tests for benzene and microbiological quality have both been adequately justified. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Based on the data submitted, a retest period could be granted of 72 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Alcohol interaction studies have been performed with the quality control (QC) method and additionally with 0.1 N HCl and no dose dumping effect has been observed. The rationale for the sort and quantity of desiccant included in the packaging are justified.

The development of the QC dissolution test is adequately discussed and the parameters are justified. For the *in vitro* dissolution tests, two different buffers have been tested, one being the QC medium. In view of the dissolution profiles of the test and reference products, the profiles are not considered similar. These differences are adequately justified based on the different composition of the test and reference product. As per guideline, the bioequivalence *in vivo* prevails; three bioequivalence studies have been performed, showing Bupropion HCl 150 mg Focus Care is bioequivalent to the reference product. These studies are discussed below in section *IV.2 Pharmacokinetics*.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines and consists of pre-blending, wet granulation, drying, milling, blending, final blending,

compression, extended release coating, delayed release coating and packaging. The manufacturing process for the tablet cores was described in sufficient detail. The coating steps are considered critical steps and the relevant process parameters' settings have been included in the description of the process. It is considered a non-standard process due to the manufacturing of a modified-release product. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

Excipients are tested and approved according to the European Pharmacopoeia (Ph.Eur.), except for the coatings, which are tested by in-house specifications, and silicified microcrystalline cellulose which is tested according to the USP-NF (National Formulary). These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of the active substance by infrared light, average tablet mass, uniformity of dosage units by mass uniformity, assay, related substances, dissolution, ethanol and microbial contamination. The latter is not routinely performed, which is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product in the HDPE container have been provided for three batches stored at 25°C/ 60% RH (24 months) 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. The product should be stored in the original bottles in order to protect from light and moisture.

In-use stability studies have been performed, based on sensitivity to moisture observed in development studies, and an in-use period of 3 months can be granted if stored below 25 °C. Updated stability studies' results and results of an in-use study performed on batches at the end of their shelf life are provided and confirm the suitability of the in-use shelf life and storage conditions. The hold time studies of the bulk tablets have been performed using two batches, which is acceptable. The bulk hold time of 3 months can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for stearic acid have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. No other products of animal origin are used.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Bupropion HCl 150 mg Focus Care has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bupropion HCl 150 mg Focus Care is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Elontril, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bupropion hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The MEB agreed that no further clinical studies are required, besides the three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Bupropion HCl 150 mg Focus Care, modified-release tablets (Focus Care Pharmaceuticals B.V., The Netherlands) was compared with the pharmacokinetic profile of the reference product Elontril 150 mg modified-release tablets (GlaxoSmithKline B.V., The Netherlands). These include: one single-dose study under fasting conditions, one single-dose study under fed conditions, and one multiple-dose study under fasting conditions. The

formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies

Study 1 – 150 mg, single dose, fasting conditions

Design

An open label, randomised, single dose, two-way crossover bioequivalence study was carried out under fasted conditions in 90 healthy subjects (52 male/ 38 female), aged 25-55 years. Each subject received a single dose (150 mg) of one of the two bupropion hydrochloride formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose (0 hours) and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 16, 20, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Eight subjects dropped out (five in period 1 and three in period 2), this left a total of 82 subjects eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bupropion hydrochloride, 150 mg under fasted conditions.

Treatment N=82	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	825.38 ±221.821	870.13 ±230.234	78.02 ±24.388	5.00 (3.00 - 12.00)
Reference	901.41 ±244.890	950.60 ±255.076	88.32 ±29.433	5.00 (3.00 - 10.50)
***Ratio (90% CI)**	0.92 (0.89 – 0.95)	0.91 (0.88 – 0.95)	0.88 (0.83 – 0.93)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – 150 mg, single dose, fed conditions

Design

An open label, randomised, single dose, two-way crossover bioequivalence study was carried out under fed conditions in 64 healthy subjects (34 male/ 30 female), aged 25-55 years. Each subject received a single dose (150 mg) of one of the two bupropion hydrochloride formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours followed by a standardised high calorie, high fat breakfast, consumed within the 30 minutes prior to the scheduled administration. There were two dosing periods, separated by a washout period of 15 days.

Blood samples were collected pre-dose (0 hours) and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 16, 20, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

The SmPC of Bupropion HCl 150 mg Focus Care states that the product can be taken with or without food. The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Four subjects dropped out in period 2, this resulted in 60 subjects being eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bupropion hydrochloride, 150 mg under fed conditions.

Treatment N=60	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	936.21 ±271.080	989.23 ±281.784	77.94 ±21.178	5.50 (4.50 - 11.00)
Reference	1005.10 ±280.432	1056.20 ±287.957	85.85 ±22.120	6.50 (4.50 - 11.00)
***Ratio (90% CI)**	0.93 (0.90 – 0.96)	0.93 (0.91 – 0.96)	0.91 (0.87 – 0.95)	

$AUC_{0-\infty}$ Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

**ln-transformed values*

Study 3 – 150 mg, multiple dose, fasting conditions

Design

An open label, randomised, steady state, two-way crossover bioequivalence study was carried out under fasted conditions in 80 healthy subjects (49 male/ 31 female), aged 25-55 years. Each subject received multiple oral doses (each 150 mg) of one of the two bupropion hydrochloride formulations, once daily, on days 0 to 8. Each tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose (0 hours) on days 0 and 6-7, and after administration of the products on day 8 at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12 and 16 hours, and on day 9 at 20 and 24 hours after administration.

The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Fourteen subjects dropped out (one in period 1 and thirteen in period 2), this left a total of 66 subjects eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bupropion hydrochloride, 150 mg under steady state conditions.

Treatment N=66	**$AUC_{0-\tau\,(ss)}$ (ng.h/mL)**	**$C_{max\,(ss)}$ (ng/mL)**	**$t_{max\,(ss)}$ (h)**
Test	935.34 ±242.694	97.77 ±32.756	4.50 (3.00 - 8.50)
Reference	997.79 ±229.833	105.13 ±25.345	5.00 (3.00 - 6.50)
***Ratio (90% CI)**	0.94 (0.90 – 0.97)	0.92 (0.87 – 0.96)	--

$AUC_{0-\tau\,(ss)}$	Area under the plasma concentration-time curve from time zero to 24 hours at steady state
$C_{max\,(ss)}$	Maximum plasma concentration in steady state
$t_{max\,(ss)}$	Time after administration when maximum plasma concentration occurs in steady state
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies

For all three studies, the 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $AUC_{0-\tau\,(ss)}$ and $C_{max\,(ss)}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Bupropion HCl 150 mg Focus Care, modified-release

tablets is considered bioequivalent with the reference product Elontril 150 mg modified-release tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 HCl 150 mg Focus Care.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	- Seizures - Increased Blood Pressure - Inappropriate route of administration
Important potential risks	- Abuse and misuse - Pancytopenia - Acute angle-closure glaucoma (US) - Increased intraocular pressure (IOP) - Arrhythmias and Conduction Disorders (potential at therapeutic doses) - Fatalities - Suicidality (Suicidal behaviour and thoughts) - Neuropsychiatric adverse events - Pregnancies – congenital cardiovascular malformations
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Elontril. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Wellbutrin XR 150 mg, modified-release tablets (NL/H/0785/001). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bupropion HCl 150 mg Focus Care, modified-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Elontril 150 mg modified-release tablets. Elontril is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bupropion HCl 150 mg Focus Care with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 6 December 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Type IB: B.I.a.1.z	Change in the manufacturer of a starting material/ reagent/ intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	No	24-3-2022	Approved	N/A
Type IB: C.I.z	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products – Other variation	Yes	2-12-2022	Approved	N/A
Type IB: B.I.b.2.e (2x); Type IA: B.I.b.2.a (4x)	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance; – Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate – Minor changes to an approved test procedure	Yes No	5-1-23	Approved	N/A