COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bupropion HCl Accord 150 mg modified-release tablets
(bupropion hydrochloride)

NL/H/4095/002/DC

Date: 6 December 2022

This module reflects the scientific discussion for the approval of Bupropion HCl Accord 150 mg modified-release tablets. The procedure was finalised at 28 June 2022. 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
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
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bupropion HCl Accord 150 mg modified-release tablets, from Accord Healthcare B.V.

The product is indicated for the treatment of major depressive episodes.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Elontril 150 mg modified-release tablets (NL RVG 33670) which has been registered in the Netherlands by GlaxoSmithKline B.V. since 10 January 2007 via decentral procedure (NL/H/0786/001-002/DC).

The concerned member states (CMS) involved in this procedure were Austria, Finland, Germany, Norway, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Bupropion HCl Accord is a creamy-white to pale yellow, round, tablet printed with "GS3" on one side and plain on the other side and contains as active substance 150 mg bupropion hydrochloride. The tablets contain a prolonged-release coating as well as a gastro-resistant coating.

The tablets are packed in oriented polyamide (OPA)/Aluminium/PVC-Aluminium blisters or perforated unit-dose blisters from the same materials.

The excipients are:
Tablet core – povidone, cysteine hydrochloride monohydrate, colloidal anhydrous silica, glycerol dibehenate and magnesium stearate (E470b).
First tablet coating – ethyl cellulose, povidone and macrogol.
Second tablet coating – methacrylic acid - ethyl acrylate copolymer (1:1) (containing sodium lauryl sulfate and polysorbate 80), colloidal hydrated silica, macrogol and triethyl citrate.
Black Printing Ink – shellac, black iron oxide (E172) and propylene glycol.

II.2 Drug Substance

The active substance is bupropion hydrochloride, an established active substance. No European Pharmacopoeia (Ph.Eur.) monograph is available but the substance is described in the United States Pharmacopoeia (USP). Bupropion hydrochloride is a white powder, soluble in water, 0.1 N hydrochloric acid and alcohol. The molecule contains a chiral centre and is manufactured as racemate. The substance is manufactured as crystalline form 1.

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

The ASMF-holder describes a synthesis route of two steps. The starting materials are acceptable in view of the recommendations in ICH Q11 and relevant EMA documents. The specifications of the starting material and the other raw materials are acceptable. The drug substance has been adequately characterised.

Quality control of drug substance

No Ph.Eur. monograph is available but the substance is described in the USP. The specification of the MAH is based on the USP monograph and ASMF-holder's specification and contains tests for description, solubility, identification, water, organic impurities, assay, chloride, residual solvents, heavy metals, residue on ignition, a specified impurity, particle size distribution, specific optical rotation and microbiological purity. The specification is acceptable. The analytical procedures have been adequately described and validated. Batch analysis results of three commercial batches have been provided, showing compliance to the specification.

Stability of drug substance

Stability data has been provided by the ASMF-holder of commercial batches of drug substance stored at long-term conditions 25°C/60% RH (six batches up to 60 months and four batches up to 18 months) and accelerated conditions 40 °C/75%RH (ten batches up to 6 months). The proposed re-test period of 1 year can be granted based on the provided data. No specific temperature restrictions are necessary. The ASMF-holder did not provide photostability data, but claimed that the substance should be stored protected from light. This is acceptable in view of the recommendation in the USP monograph (preserve in well-closed, light-resistant containers. Store at room-temperature).

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. The development of the formulation of the modified-release tablets has been adequately explained. The functions of the excipients have been stated and a summary of development trials to obtain the optimized final formulation has been given.

Bioequivalence studies have been performed (see section IV. *Clinical aspects*). The test product as used in the bioequivalence studies is representative of the commercial product in view of the formulation, batch size and manufacturing process. Complementary dissolution studies have been performed with the batches as used in the studies in three media (0.1 N hydrochloric acid, acetate buffer pH 4.5 and phosphate buffer pH 6.8). The specification limits have been adjusted to be in line with the guideline "*Quality of oral modified release products*" and the analytical method for dissolution was adequately validated. No change to the manufacturing process was necessary in order to obtain product compliance with the updated dissolution limits.

Results for dissolution of the bio-batch were not similar to the reference product, however this discrepancy has been adequately discussed. Namely, the *in vivo* results prevail, as the performed studies showed bioequivalence between the test and reference products. Therefore, this was acceptable.

Development of the manufacturing process is briefly explained and is performed in line with formulation development. An acceptable elemental impurity risk assessment according to ICH Q3D is provided.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. A description of the manufacturing process (wet granulation followed by drying, sizing, blending, compression and two coating steps) is acceptable as it contains sufficient details. Sufficient information on critical process parameters is provided. The requested holding time for bulk tablets is acceptable. The process has been validated on three commercial scale batches and is considered a non-standard process.

Control of excipients

The analytical procedures and specifications for the in-house tests have been adequately described and validated. The specifications of the pharmacopoeial excipients were accepted after the MAH, in response to questions, provided details on the tests, limits and analytical procedures.

Quality control of drug product

The specification of the drug product contains tests for description, average weight of tablets, identification, water content, dissolution, uniformity of dosage units, organic

impurities, assay, residual solvent and microbial purity. The release and shelf-life specification are identical and are based on the USP monograph of Bupropion extended release tablets. The specification is acceptable, the dissolution limits reflect the results of the batch used in the bioequivalence study. The analytical procedures have been adequately described and validated. Sufficient batch analysis results have been provided, showing compliance to the proposed specification. The organic impurities have been discussed in line with those mentioned in the USP monograph of bupropion hydrochloride extended release tablets.

The risk evaluation on nitrosamine impurities is acceptable, also because this is a line extension from a previously approved drug product (Bupropion 300 mg modified-release tablets, NL/H/4095/001/DC) with the same excipients and the same packaging material. There are no new risks associated with the 150 mg strength.

Stability of drug product

Stability data of three batches of commercial product have been stored at long-term conditions of 25°C/60% RH (one batch up to 24 months and two batches up to 12 months) and accelerated conditions of 40°C/75% RH (up to 6 months) in OPA/Alu/PVC-Alu blisters. A shelf-life period of 2 years could be granted, based on the provided data. Storage restrictions are not considered necessary. A photostability study has been performed and show that the product is not sensitive to light.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bupropion HCl Accord 150 mg modified-release tablets 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 Accord 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 member states 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 overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required besides the bioequivalence studies.

For this generic application, the MAH has reported three bioequivalence studies: a single dose study under fasting conditions, a single dose study under fed conditions, and a multiple dose study under fasting conditions.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Bupropion HCl Accord 150 mg modified-release tablets (Accord Healthcare B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Elontril 150 mg modified-release tablets (GlaxoSmithKline B.V., the Netherlands).

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products . The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Study 1 – single dose, fasting, 150 mg

Design

An open label, balanced, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 19 – 43 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 a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 16, 20, 24, 36, 48, 72 and 96 hours after administration of the products.

According to the SmPC, the product may 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 were withdrawn from the study: one subject was withdrawn on the grounds of emesis in Period-I, one subject was withdrawn on medical grounds in Period-II, one subject was withdrawn on the grounds of protocol noncompliance in Period-II and one subject discontinued from the study on his own accord in Period-II. This left 28 subjects eligible for pharmacokinetic analysis.

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

Treatment N=28	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	815 ± 298	859 ± 308	68.9 ± 24.3	7.50 (4.00 – 14.00)
Reference	754 ± 321	793 ± 329	65.8 ± 29.7	5.00 (2.50 – 7.50)
***Ratio (90% CI)**	1.11 (0.98 – 1.25)	1.11 (0.99 – 1.25)	1.08 (0.94 – 1.24)	--

$AUC_{0-\infty}$ 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 t hours (time of the last measurable plasma concentration)
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
* ln-transformed values

Study 2 – single dose, fed, 150 mg

Design

An open label, balanced, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover bioequivalence study was carried out under fed conditions in 80 healthy male subjects, aged 19 – 44 years. The subjects were divided into three groups, which underwent the study in identical manners. 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 high fat high calorie breakfast which was consumed within 30 minutes (consisting of bread, butter, chana, onions, peanuts, oil, potatoes, cheese, paneer, milk and sugar). There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 16, 20, 24, 36, 48, 72 and 96 hours after administration of the products.

According to the SmPC, the product may 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

In group I, two subjects dropped out (one for emesis in Period I, and one stopped on his own accord in Period II). In group II, two subjects were replaced with backup subjects before dosing in Period I and two subjects dropped out: one withdrew on his own accord in period II, and one was withdrawn on medical grounds in Period II. In group III, all subjects completed the study. This left 76 subjects eligible for pharmacokinetic analysis.

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

Treatment N=76	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	811 ± 217	852 ± 224	78.5 ± 21.3	5.50 (3.00 – 10.00)
Reference	761 ± 255	799 ± 260	81.1 ± 27.1	6.00 (2.00 – 10.00)
***Ratio (90% CI)**	1.08 (1.03 – 1.13)	1.08 (1.03 – 1.13)	0.98 (0.93 – 1.05)	--

$AUC_{0-\infty}$	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 t hours (time of the last measurable plasma concentration**)**
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
*	ln-transformed values

Study 3 – multiple dose, fasting, 150 mg

Design

An open label, balanced, randomised, two-sequence, two-treatment, two-period, multiple oral dose, full replicate, bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 20 – 44 years. Each subject received a single dose (150 mg) of one of the two bupropion hydrochloride formulations. The tablet was orally administered from Day 1 to Day 11, with 240 mL water after an overnight fast of at least 10 hours. The dosing moments had an interval of 24 hours. There were two dosing periods, separated by a washout period of 20 days.

Blood samples were collected pre-dose on Day 01, 08, 09 and 10, and post-dose on Day 10 (and Day 11), at the time of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 16, 20 and 24 hours after administration of the products.

According to the SmPC, the product may 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: one stopped on his own accord in Period I, two were withdrawn due to emesis in Period I and one was withdrawn due to medical reasons in Period II. This left 28 subjects in total eligible for pharmacokinetic analysis.

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

Treatment N=28	**$AUC_{0-\tau,ss}$ (ng.h/mL)**	**$C_{max,ss}$ (ng/mL)**	**$C_{\tau,ss}$ (ng/mL)**	**$t_{max,ss}$ (h)**
Test	903 ± 301	94.1 ± 36.6	13.6 ± 5.3	5.00 (3.00 – 12.00)
Reference	912 ± 296	94.9 ± 30.8	14.6 ± 5.6	5.00 (3.00 – 10.00)
***Ratio (90% CI)**	0.99 (0.94 – 1.04)	0.98 (0.91 – 1.04)	0.93 (0.87 – 0.99)	--

$AUC_{0-\tau,ss}$	area under the plasma concentration curve during a dosage interval at steady state (τ=24h)
$C_{max,ss}$	maximum plasma concentration at steady state
$C_{\tau,ss}$	concentration at the end of the dosing interval at steady state (τ=24h)
t_{max}	time for maximum concentration
*	ln-transformed values

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $AUC_{0-\tau,ss}$, $C_{max,ss}$ and $C_{\tau,ss}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies, Bupropion HCl Accord 150 mg modified-release tablets is considered bioequivalent with 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 Accord.

Table 4. Summary of safety concerns as approved in RMP

Important identified risks	• Seizures • Inappropriate route of administration • Increased blood pressure
Important potential risks	• Arrhythmias and conduction disorders (potential at therapeutic doses) • Fatalities • Suicidality • Smoking cessation aids and neuropsychiatric adverse events • Pregnancies-congenital cardiovascular malformations • Increased intraocular pressure (IOP) • Acute angle-closure glaucoma • Bupropion abuse and misuse • Pancytopenia
Missing information	None

The member states 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 Elontril 150 mg modified-release tablets (NL RVG 33670) for content, and to Mycophenolic acid Accord 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC) for design, layout and style of writing. 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 Accord 150 mg 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.

In the Board meeting of 25 May 2022, the dissolution specification was discussed as it was not yet in line with the guideline. This issue was adequately discussed and considered resolved before the end of the procedure.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bupropion HCl Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 June 2022.

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
N/A	N/A	N/A	N/A	N/A	N/A