COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bupropion HCl Sandoz retard 300 mg, modified-release tablets (bupropion hydrochloride)

NL/H/3042/003/DC

Date: 5 January 2023

This module reflects the scientific discussion for the approval of Bupropion HCl Sandoz retard 300 mg, modified-release tablets. The procedure was finalised on 20 July 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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bupropion HCl Sandoz retard 300 mg, modified release tablets, from Sandoz 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 300 mg modified-release tablets (NL RVG 33671) by GlaxoSmithKline B.V., registered in the Netherlands since 10 January 2007 via a decentralised procedure (NL/H/0786/002).

The concerned member state (CMS) involved in this procedure was Austria.

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

II. QUALITY ASPECTS

II.1 Introduction

Bupropion HCl Sandoz retard is a creamy-white to pale yellow, round tablet, printed with "GS2" on one side and plain on the other side.

Each modified-release tablet contains as active substance 300 mg of bupropion hydrochloride.

The tablets are packed in oriented polyamide (OPA)/Aluminium/PVC-Aluminium blisters.

The excipients are:
Tablet core – povidone, cysteine hydrochloride monohydrate, colloidal anhydrous silica, glycerol dibehenate and magnesium stearate.
Tablet coating – ethyl cellulose, povidone, colloidal hydrated silica, methacrylic acid-ethyl acrylate copolymer (1:1), sodium lauryl sulphate, polysorbate 80, macrogol and triethyl citrate.
Printing ink – shellac glaze, black iron oxide (E172), propylene glycol and ammonium hydroxide 28%.

II.2 Drug Substance

The active substance is bupropion hydrochloride (HCl), an established active substance described in the United States Pharmacopoeia (USP). Bupropion HCl 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 also 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 manufacturing process consists of a synthesis route of two steps. The starting materials are acceptable in view of the recommendations in ICH guideline Q11 and relevant EMA documents. The specifications of the starting materials and the other raw materials are acceptable. The drug substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the USP and in-house specifications of the ASMF holder. The analytical procedures have been adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scaled batches.

Stability of drug substance

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance at long-term conditions 25°C/60% RH (six batches up to 60 months) and accelerated conditions 40°C/75% RH (six batches up to 6 months). The substance should be stored in well-closed, light-resistant containers at room-temperature, in view of the recommendation in the USP monograph.

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 functions of the excipients have been explained and a summary of development trials to obtain the optimised final formation has been given. The test product used in the bioequivalence studies is representative of commercial product in view of the formulation, batch size, assayed content and manufacturing process. Complementary dissolution studies have been performed with the batches as used in the bioequivalence studies in three media (0.1 N HCl (quality control medium), acetate buffer pH 4.5 and phosphate buffer pH 6.8), demonstrating comparability in all three media. The MAH has investigated the modified release *in vitro* in 5%, 20 % and 40% alcohol, which showed that at alcohol concentrations of

20% and higher, bupropion is released rapidly (up to 20% dissolved at 2 hours). A statement regarding this is included in the SmPC.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines and is considered non-standard. Process validation data on the product have been presented for three commercial size batches in accordance with the relevant European guidelines. The process includes wet granulation followed by drying, sizing, blending, compression and two coating steps.

Control of excipients

The excipients are not novel. The pharmacopoeial excipients will be tested in accordance with the relevant monograph in the current editions of the Ph.Eur. and the USP-National Formulary (NF) and the excipients which are not official in the Ph.Eur. or USP-NF will be tested with the in-house specification and method of analysis procedures. The specifications of the in-house excipients are acceptable. The analytical procedures have been adequately described. 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 description, average weight of tablets, identification (infrared and high-pressure liquid chromatography), water content, dissolution, uniformity of dosage units, organic impurities, assay, residual solvent and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life specification are identical and are based on the USP monograph.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from six batches from the proposed production site have been provided, demonstrating compliance with the specification. An acceptable elemental impurity risk assessment according to ICH guideline Q3D is provided. A risk assessment on the potential presence of nitrosamines in the drug product is provided; this is acceptable.

Stability of drug product

Three (small) batches have been stored at long-term conditions of 25°C/60% RH (up to 36 months) and accelerated conditions of 40°C/75% RH (up to 6 months). Furthermore, stability data up to 12 months at long term conditions are available for one full scale batch. A claimed shelf-life of 2 years is acceptable. The product does not require special storage restrictions and the product is not sensitive to light as shown in a photostability study.

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 Sandoz retard 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 Sandoz retard 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 HCl 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 three bioequivalence studies submitted by the MAH, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product Bupropion HCl Sandoz retard 300 mg, modified release tablets, from Sandoz B.V. is compared with the pharmacokinetic profile of the reference product Elontril 300 mg modified-release tablets by GlaxoSmithKline B.V.

The choice of the reference product in the bioequivalence study 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, 300 mg, fasted

Design

A open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 79 healthy male subjects, aged 18 – 44 years. Each subject received a single dose (300 mg) of one of the two bupropion 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 24 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, 96, 120 and 144 hours after administration of the products. The SmPC states that Bupropion HCl Sandoz retard (300 mg) 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

Ten subjects did not complete the study (eight discontinued from the study on their own accord in Period-II and two were withdrawn from the study due to protocol non-compliance in Period-II). This resulted in a total of 69 subjects being eligible for pharmacokinetic analysis.

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

Treatment N=69	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	2144 ± 780	2206 ± 845	207 ± 79	5.5 (3.5 - 12)
Reference	2229 ± 711	2283 ± 723	199 ± 56	5.0 (3.0 - 10)
***Ratio (90% CI)**	0.95 (0.89 – 1.00)	0.95 (0.89 – 1.00)	1.00 (0.94 – 1.06)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last measurable concentration at time t
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**ln-transformed values*

Study 2 – single dose, 300 mg, fed

Design

A open label, balanced, randomised, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study was carried out under fed conditions in 60 healthy male subjects, aged 19 – 44 years. Each subject received a single dose (300 mg) of one of the two bupropion formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours followed by a high-calorie, high-fat, vegetarian breakfast, consumed within the 30 minutes before dosing. There were two dosing periods, separated by a washout period of 18 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, 96, 120 and 144 hours after administration of the products.

The SmPC states that Bupropion HCl Sandoz retard (300 mg) 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

Six subjects did not complete the study (four subjects discontinued from the study on their own accord in Period-II, one subject was withdrawn on medical grounds in Period-II and one subject was withdrawn due to protocol non-compliance in Period-II). This resulted in a total of 54 subjects being eligible for pharmacokinetic analysis.

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

Treatment N=54	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h
Test	2166 ± 427	2216 ± 430	233 ± 66	7.0 (4.0 - 14.0)
Reference	2122 ± 534	2168 ± 534	202 ± 55	6.0 (2.5 - 16.0)
***Ratio (90% CI)**	1.03 (0.99 - 1.08)	1.03 (0.99 – 1.08)	1.15 (1.07 – 1.24)	--

AUC_{0-t} Area under the plasma concentration curve from administration to last measurable concentration at time t
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**ln-transformed values*

Study 3 – multiple dose, 300 mg, fasted

Design

An open-label, multiple-dose, randomised, two-period, two-treatment, fully replicate, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 19 – 44 years. Each subject received one dose (300 mg) of one of the two bupropion formulations on Day 1 to Day 11. 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 17 days.

Blood samples were collected pre-dose on Day 01, 08, 09 and 10, and post-dose on Day 10 and Day 11 at 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.

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. An apparent raise in plasma levels was found on Day 8, 9 and 10, but since these levels lowered again at Day 10 and 11, it was concluded that steady state was indeed achieved at Day 7, which was also consistent with the half-life of bupropion (~20 hours). Therefore, this was acceptable.

Results

Seven subjects did not complete the study (two subjects were withdrawn from the study on medical grounds in Period-I, one discontinued on his own accord in Period-I, three were withdrawn on medical grounds in Period-II, and one subject discontinued on his own accord in Period-II). This resulted in 37 subjects being eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bupropion under steady state, fasted conditions (n=37, 74 observations).

Treatment N=37	**$AUC_{0-\tau,ss}$** ng.h/ml	**$C_{max,ss}$** ng/ml	**$C_{\tau,ss}$** ng/ml	**$t_{max,ss}$** h
Test	1746 ± 529	190 ± 73	30 ± 10	5.5 (3.0 - 9.0)
Reference	1792 ± 497	173 ± 49	33 ± 11	4.8 (3.0 - 9.0)
***Ratio (90% CI)**	0.96 (0.92 – 1.01)	1.07 (1.01 – 1.14)	0.89 (0.84 – 0.94)	--

$AUC_{0-\tau,ss}$	Area under the plasma concentration curve during a dosage interval (24 h) at steady state
$C_{max,ss}$	Maximum plasma concentration at steady state
$C_{t,ss}$	Concentration at the end of the dosing interval (24 h) at steady state
$t_{max,ss}$	Time until $C_{max,ss}$ is reached

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies, Bupropion HCl Sandoz retard 300 mg is considered bioequivalent with Elontril 300 mg.

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 Sandoz retard.

Table 4. Summary 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 • 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 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 the 150 mg Bupropion HCl Sandoz (NL/H/3041/001) and to Wellbutrin XR 150 and 300 mg modified release tablets (NL/H/0785/001-002). 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 Sandoz retard 300 mg, modified release tablets has a proven chemical-pharmaceutical quality and is a generic form of Elontril 300 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bupropion HCl Sandoz retard (300 mg) with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 July 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