COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bupropion HCl retard Teva 300 mg, modified-release tablets

(bupropion hydrochloride)

NL/H/4426/001/DC

Date: 7 March 2019

This module reflects the scientific discussion for the approval of Bupropion HCl retard Teva 300 mg, modified-release tablets. The procedure was finalised at 10 September 2018. 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 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 retard Teva 300 mg, modified-release tablets, from Teva 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 which has been registered in the Netherlands by GlaxoSmithKline B.V. since 10 January 2007 through decentralised procedure NL/H/0786/002.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Bupropion HCl retard Teva is a creamy-white to pale yellow, round, tablet printed with "GS2" on one side and plain on the other side. Each tablet contains 300 mg bupropion hydrochloride.

The modified-release tablets are packed in OPA/Alu/PVC-Alu blisters and OPA/Alu/PVC-Alu perforated unit dose blisters.

The excipients are:
Tablet core – povidone, cysteine hydrochloride monohydrate, silica, colloidal anhydrous , glycerol dibehenate and magnesium stearate (E470b)
First tablet coating – ethyl cellulose 100 mPas, povidone and macrogol
Second tablet coating – methacrylic acid (ethyl acrylate copolymer (1:1) (containing sodium laurylsulfate and polysorbate 80)), colloidal hydrated silica, macrogol and triethyl citrate
Printing ink (black) – 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 Pharmacopeia (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 also manufactured as crystalline Form I.

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 proposes a synthesis route of two steps. The starting materials are in view of ICH recommendations and relevant EMA documents. The specifications of the 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 is based on the USP monograph/ASMF-holders specification and contains tests for description, solubility, identification, water, organic impurities, assay, chloride, residual solvents, heavy metals, residue on ignition, impurity of an intermediate, particle size distribution, specific optical rotation and microbiological purity. The specification is acceptable. The analytical procedures have been adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three commercial batches.

Stability of drug substance

Stability data on the active substance have been provided for six batches stored at 25°C/60% RH (three batches up to 60 months, three batches up to 36 months) and accelerated conditions 40 °C/75%RH (up to 6 months). Based on the data submitted, a retest period could be granted of one year when stored. No specific temperature restrictions are necessary. Although the ASMF-holder has not provided photostability data however claims 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 functions of the excipients have been stated and a summary of development trials to obtain the optimized final formation has been given.

Bioequivalence studies have been performed. The test product as used in these studies is representative of 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 bioequivalence studies in three media (0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8). Development of the manufacturing process is briefly explained and is performed in line with formulation development. An acceptable elemental impurity risk assessment according to the ICH guideline 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 generally acceptable as it contains sufficient details. Sufficient information on critical process parameters is provided. The holding times are acceptable. Validation data on the product have been presented for three commercial batches in accordance with the relevant European guidelines.

Control of excipients

The pharmacopoeial excipients will be tested in accordance with the relevant monograph in the current editions of Ph.Eur./USNF and the excipients which are not official in Ph.Eur/USNF will be tested with the in-house specification and method of analysis. 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, 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. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial batches stored at 25°C/60% RH (up to 24 months) and 40 °C/75 RH (up to 6 months). The batches were stored in the proposed packaging. The product is not sensitive to light as shown in a photostability study. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions need to be included in the SmPC or on the label.

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 retard Teva 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 retard Teva 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.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Bupropion HCl retard Teva 300 mg, modified-release tablets (Teva B.V., NL) is compared with the pharmacokinetic profile of the reference product Elontril 300 mg modified-release tablets (GlaxoSmithKline B.V., NL).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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.

Bioequivalence studies

Study I – 300 mg under fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 79 healthy male subjects, aged 18-45 years. Each subject received a single dose (300 mg) of one of the 2 bupropion formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 24 days.

Blood samples were collected pre-dose and at 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0, 120.0 and 144.0 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-life. Also the washout period is acceptable.

Results
Eight subjects withdrew from the study on their own accord and two subjects were withdrawn from the study on the grounds of protocol non-compliance. Therefore, 69 subjects were 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)	--

$AUC_{0-\infty}$ 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
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Study II – 300 mg under fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 18-45 years. Each subject received a single dose (300 mg) of one of the 2 bupropion formulations. The tablet was orally administered with 240 ml water within 30 minutes after after a high fat and high calorie vegetarian breakfast. There were 2 dosing periods, separated by a washout period of 18 days.

Blood samples were collected pre-dose and at 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, 48.0, 72.0, 96.0, 120.0 and 144.0 hours after administration of the products.

The overall study design is considered acceptable considering the absorption rate and half-life of 20 hours. Also the quantity and composition of breakfast and the washout period are acceptable.

Results

Four subjects withdrew from the study on their own accord, one subject was withdrawn on medical grounds and one subjects on ground of protocol non-compliance. Therefore, 54 subjects completed the study and were 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)	--

$AUC_{0-\infty}$	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
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration

**ln-transformed values*

Study III – multiple-dose 300 mg under steady-state fasting conditions

Design

A open-label, multiple-dose, randomised, two-period, two-treatment, fully replicate, crossover bioequivalence study was carried out under steady-state fasted conditions in 44 healthy male/female subjects (mean age 30.9). Each subject received a single dose (300 mg) of one of the 2 bupropion formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Either the test or reference product was administered from day 1 to day 11. There were 2 dosing periods, separated by a washout period of 17 days.

On day 1, 8, 9 and 10 pre-dose samples were withdrawn immediately prior to each dose with an allowed deviation of -05 minutes in each period. On day 10 and 11 blood samples were collected at the scheduled time at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 20.0 and 24.0 hours post-dose in each period.

The design of the study is acceptable. A wash-out period of 17 days (i.e. at least 5 terminal half-lives) is sufficient to exclude carry-over effects in accordance to the guideline.

Results

Five subjects were withdrawn from the study on medical grounds and two subjects withdrew on their own accord. Therefore, 37 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=37	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (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 (1.02 – 1.14)	0.89 (0.84 – 0.94)	--

$AUC_{0-\infty}$	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
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence studies

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

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

Important identified risks	- Seizure - 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 a bioequivalence study 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 300 mg modified-release tablets. 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 retard Teva 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 retard Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 September 2018.

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