COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bupropion HCl retard Teva 150 mg, modified-release tablets

(bupropion hydrochloride)

NL/H/4484/001/DC

Date: 5 December 2019

This module reflects the scientific discussion for the approval of Bupropion HCl retard Teva. The procedure was finalised on 3 October 2019. 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
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 150 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 150 mg modified-release tablets (NL Licence RVG 33670) which has been registered in the Netherlands by GlaxoSmithKline BV since 10 January 2007 through decentralised procedure NL/H/0786/001.

The concerned member states (CMS) involved in this procedure were Germany, Luxembourg, Portugal and Spain.

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 150 mg is a creamy white to pale yellow, round, biconvex tablet. Each tablet contains bupropion hydrochloride 150 mg.

The modified-release tablets are packed in plastic bottles (HDPE) with a sealed child-resistant plastic cap (PP closure) with desiccant integrated in the cap.

The excipients are:
Core - hydroxypropyl Cellulose (353-658 mPa) (E463) (contains silicon dioxide), silicified microcrystalline cellulose, stearic acid (type 50), magnesium stearate, purified water
First coating - ethyl cellulose (E462), hydroxypropyl cellulose, titanium dioxide (E171), triethyl citrate (E1505)
Second coating - methacrylic acid – ethyl acrylate copolymer, talc (E553b)

II.2 Drug Substance

The active substance is bupropion hydrochloride, an established active substance described in the United States Pharmacopoeia (USP). It is not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white powder, which is freely soluble in

methanol, soluble in water and ethanol and 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 HCl 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.
Bupropion HCl has been adequately characterized and acceptable specifications for the starting material and the other solvents and reagents used in the manufacturing process have been adopted.

Quality control of drug substance

The active substance specification of the MAH has been established based on the ASMF and includes tests for description, identification, water, assay, related substances, residual solvents and additional requirements for particle size. The specification is acceptable.
In-house methods were adequately described and validated. Batch analytical data demonstrating compliance with the active substance specification have been provided for three batches.

Stability of drug substance

All investigated stability parameters are within specifications after up to 72 months storage at 25°C and 6 months storage at 40°C. A re-test period of 6 years has therefore been granted, when stored in the commercial packaging. No storage restriction is warranted based on presented stability data.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The goal of the formulation development was to understand the effect of excipients on the formulation, demonstrated with dissolution profiles. A summary describing the development of the formulation is provided. In addition, studies on the effect of moisture on assay and impurities have been performed which result in a storage restriction regarding protection from moisture.

Alcohol interaction studies have been performed with the QC method and additionally with 0.1 N HCl and no dose dumping effect has been observed.
Three bioequivalence studies have been performed using the 150 mg modified-release tablet vs the 150 mg modified-release tablet reference product.
For the *in vitro* dissolution tests two different buffers have been tested (one is also the QC medium), pH 1.2 0.1N HCl followed by pH 6.8 buffer with 0.05% SLS and pH 4.5 buffer followed by pH 6.8 buffer with 0.05% SLS. In view of the dissolution profiles of the test and reference products, the profiles are not considered similar. Possible reasons for the discrepancy have been discussed. This is accepted as per bioequivalence guideline CPMP/QWP/EWP/1401/98 Rev.1 it is stated that 'In the event that the results of comparative *in vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated *in vivo* the latter prevails'. Hence successful bioequivalence has been demonstrated.

Manufacturing process
The manufacturing process 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 core tablets 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. The process has been adequately validated on three batches of commercial size.

Control of excipients
Excipients are tested according to the Ph.Eur, except for the coatings (in-house) and silicified microcrystalline cellulose which is tested according to the USP-NF. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of the active substance by IR, average tablet mass, uniformity of dosage units, assay, impurities, dissolution, ethanol and microbial contamination. The latter is not routinely performed, which is acceptable. The release and shelf life specifications are identical except for average tablet mass and impurities. The dissolution limits in the QC method are set based on the results of the biobatch. Analytical methods were described and validated.
Batch analysis data showing compliance with the release specification were provided on three commercial-scale batches.

Stability of drug product
Stability data on the drug product was provided for three production batches stored at 25°/60% RH (18 months), 30°C/75% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Statistical analysis has been performed to allow extrapolation.
A photostability study has been submitted, in accordance with ICH Q1B. Results indicate that the drug product is not in compliance with the specification after exposure to light,

therefore the drug product is considered not photostable.
Based on the data of 18 months and the statistical evaluation, a shelf-life period of 24 months has been granted. The product should be stored in the original bottles in order to protect from light and moisture. In-use stability studies have also been performed. Based on sensitivity to moisture in development studies, an in-use period of 3 months has been granted if stored below 25 °C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM 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. One excipient of animal origin is used in the formulation of the drug product: stearic acid. The supplier confirmed that stearic acid is BSE/TSE free.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Bupropion HCl retard Teva 150 mg 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 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.

For this generic application, the MAH has submitted 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 retard Teva 150 mg (Teva B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Elontril 150 mg modified-release tablets (GlaxoSmithKline GmbH & Co. KG, Germany). The first study was a study under fasting conditions in healthy volunteers and the second a study under fed conditions in healthy volunteers. The third study was a multiple-dose fasting study in healthy volunteers.

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 methods used in the studies have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence was investigated under fed, fasted and multiple-dose conditions as is required for a modified-release formulation in accordance with the guidelines.

Bioequivalence studies

Bioequivalence study I – single-dose, fasted
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 90 healthy subjects (52 males, 38 females), aged 25-55 years. Each subject received a single dose (150 mg) of one of the 2 bupropion HCl formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre-dose 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. The start and the duration of the sampling is sufficient to measure pharmacokinetic parameters considering the t_{max} and half-life (approximately 5h and 20h, respectively) of bupropion. A washout period of 14 days (i.e. at least 5 terminal half-lives) is sufficient to exclude carry-over effects in accordance to the guideline.

Results
In period 1 five subjects dropped out:
- one subject withdrew consent for personal reasons.
- two subjects were early terminated due to an adverse event.
- one subject was early terminated due to positive alcohol screen.
- one subject was early terminated due to positive drug screen.

In period 2 three subjects dropped out:
- one subject was early terminated due to contraband found on admission.
- one subject withdrew consent due to personal reasons.
- one subject was early terminated due to positive pregnancy on period 2 admission.

The remaining eighty-two 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=82	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	826 ± 222	870 ± 230	78 ± 24	5.0 (3.0-12.0)	--
Reference	901 ± 245	951 ± 255	88 ± 29	5.0 (3.0-10.5)	--
***Ratio (90% CI)**	0.92 (0.89-0.95)	0.91 (0.88- 0.95)	0.88 (0.83- 0.93)	--	--
CV (%)	13.59	13.05	21.50	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II – single-dose, fed

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 64 healthy subjects (34 males, 30 females), aged 25-55 years. Following an overnight fast of at least 10 hours, subjects were served a standard test meal (standardized high calorie, high fat breakfast) 30 minutes prior to scheduled administration of the investigational product. The test meal provided to the subjects complies with the requirements given in the guideline with a total o of 910 calories of which 52% derived from fat. Exactly 30 minutes after start of the test meal which was consumed entirely, a single oral dose (bupropion 150 mg prolonged release tablet) was administered with 240 ml of water. There were 2 dosing periods, separated by a washout period of 15 days.

Blood samples were collected at pre-dose 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 study design is acceptable. The start and the duration of the sampling is sufficient to measure pharmacokinetic parameters considering the t_{max} and half-life (approximately 5h and 20h, respectively) of bupropion. A wash-out period of 15 days (i.e. at least 5 terminal half-lives) is sufficient to exclude carry-over effects in accordance to the guideline.

Results

In period 1 four subjects dropped out:

- three subjects withdrew consent for personal reasons.
- one subject was early terminated due to an adverse event (emesis).

In period 2 no subjects dropped out. The remaining sixty subjects 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=60	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	936 ± 271	989 ± 282	78 ± 21	5.5 (4.5-11.0)	--
Reference	1005 ± 280	1056 ± 288	86 ± 22	6.5 (4.5-11.0)	--
***Ratio (90% CI)**	0.93 (0.90- 0.96)	0.93 (0.91-0.96)	0.91 (0.87- 0.95)		--
CV (%)	9.95	9.86	14.30	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Bioequivalence study III – multiple-dose, fasted

Design

An open label, randomised, two-treatment, two-period, two-sequence, multiple-dose, crossover bioequivalence study was carried out under fasted conditions in 80 healthy subjects (49 males, 31 females), aged 25-55 years.

In each study period, following an overnight fast of at least 10 hours, multiple oral doses of investigational products (bupropion 150 mg modified-release tablet) of either the test product or the reference product were administered with 240 mL of water at the same time of the day, once daily in the morning on days 0 to 8. A washout period of 14 days was maintained between the successive dosing days.

The pre-dose blood sample was collected within five minutes before dosing.
Day 0, 6-7: Pre-dose samples were collected prior to dosing.
Day 8: Pre-dose sample and samples were collected 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 and 24 hours following medication administration in each period.

The study design is acceptable. Steady State of bupropion and its metabolites is reached within 8 days. The start and the duration of the sampling is sufficient to measure pharmacokinetic parameters considering the t_{max} and half-life (approximately 5h and 20h, respectively) of bupropion. A wash-out period of 14 days (i.e. at least 5 terminal half-lives) is sufficient to exclude carry-over effects in accordance to the guideline.

Results

A total of 14 subjects dropped out of the study.

In period 1 two subjects dropped out:

- one subject was early terminated due to Serious Adverse Event (SAE).
- one subject was early terminated due to an adverse event.

In period 2 twelve subjects dropped out:

- three subjects were early terminated due to an adverse event.
- three subjects did not show up for period 2 admission.
- four subjects withdrew consent for personal reasons.
- two subjects were early terminated due to positive urine drug screening at admission period 2.

The remaining sixty-six subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters in steady state (non-transformed values; arithmetic mean ± SD)

Treatment N=66	**AUC_τ** (ng/ml/h)	**C_{max}** (ng/ml)	**C_{min}** (ng/ml)	**PTF%** (%)
Test	935 ± 243	98 ± 33	21 ± 8	4.5 (3.0-8.5)
Reference	998 ± 230	105 ± 25	18 ± 6	5.0 (3.0-6.5)
***Ratio (90% CI)**	0.94 (0.90-0.97)	0.92 (0.87-0.96)	1.15 (1.11-1.20)	--
CV (%)	11.67	16.74	21.24	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index
CV coefficient of variation

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and $C_{max,}$ as well as AUC_τ, C_{max} and C_{min} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Bupropion HCl retard Teva 150 mg is considered bioequivalent with Elontril 150 mg modified-release tablets, under fasted conditions, fed conditions and in steady state.

Safety

Based on the review of the clinical and laboratory safety data, both the test and reference product were found to be safe and well tolerated in all three bioequivalence studies.

The MEB has been assured that the bioequivalence studies have 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 150 mg.

Table 4. Summary table 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 - 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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bupropion HCl retard Teva 150 mg, modified-release tablets has a proven chemical-pharmaceutical quality and is a generic form of Elontril 150 mg. 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 3 October 2019.

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