CBG MEB

Public Assessment Report

Scientific discussion

Bupropion HCl Sandoz retard 150 mg and 300 mg, modified-release tablets

(bupropion hydrochloride)

NL/H/3041/001-002/DC

Date: 29 September 2015

This module reflects the scientific discussion for the approval of Bupropion HCl Sandoz retard 150 mg and 300 mg, modified-release tablets. The procedure was finalised on 5 March 2015. For information on changes after this date please refer to the module 'Update'.

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 150 mg and 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 150 mg and 300 mg modified-release tablets which have been registered in the Netherlands by GlaxoSmithKline B.V. since 2007 through decentralised procedure NL/H/0786/001-002.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Finland, Germany, Luxembourg, Portugal, Slovenia, 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 Sandoz retard 150 mg is a white to pale yellow, round, biconvex tablet, plain on both sides.
Bupropion HCl Sandoz retard 300 mg is a white to pale yellow, biconvex tablet, printed with 'A 152' on one side and plain on the other side.

The modified-release tablets are packed in white opaque high density polyethylene (HDPE) bottles closed with a child-resistant cap containing silica gel.

The excipients are:
Tablet core – povidone, hydrochloric acid, sodium stearyl fumarate
Tablet coating **–** ethylcellulose, hydroxy propylcellulose, methacrylic acid-ethyl acrylate copolymer (1:1) Type A, colloidal anhydrous silica, macrogol 1500, triethyl citrate, hypromellose, macrogol 400, macrogol 8000
Printing ink **–** shellac glaze, iron oxide black (E172), propylene glycol, ammonium hydroxide

The core of the two tablet strengths is dose proportional.

II.2 Drug Substance

Bupropion hydrochloride is an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.) or British Pharmacopoeia, nor mentioned in the EDQM knowledge database. A monograph on bupropion hydrochloride is included in the Pharmacopoeia of the United States (USP). Bupropion HCl is a white powder which is soluble in water, 0.1N hydrochloric acid and in alcohol. It has a bitter taste and produces the sensation of local anaesthesia on the oral mucosa. The manufacturer produces the racemate. Bupropion does not show any polymorphism as per the available literature.

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 described process comprises five synthesis steps and one purification step. The defined starting material of the synthesis is acceptable. The discussion on potential impurities, including potential genotoxic impurities is appropriate.

Quality control of drug substance
The control tests and specifications for the drug substance are adequately drawn up. The MAH applies the drug specifications of the ASMF with additional tests for particle size distribution, bulk density and microbial limits. Results of batch analysis have been provided of three production scale batches, demonstrating compliance with the specification.

Stability of drug substance
The proposed re-test of 18 months has been adequately supported by submitted stability results of three production scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months).

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been adequately performed and described, the choice of excipients is justified and their functions explained. Some of the applied excipients differ from the reference product, yet are usual for oral dosage forms. The tablets have a triple coating layer, the outer layer is hydrophilic and easily dissolved, the middle layer is gastro-resistant and the inner layer prolonged release.
It is indicated that the child resistant cap complies with the “CFR 16 part 1700” and “Therapeutic Goods Order No. 80 Child-Resistant Packaging Requirements for Medicines” and the conformation certificate has been provided. It is not certified to the ISO 8317 standard. However, both standards are very similar with the CFR16 Part 1700 standard being a little more stringent over that of the ISO8317 standard. Child safety of the closure has been adequately demonstrated.
The proposed particle size distribution specification has been justified based on the particle size distribution of the active substance batches that were used for the manufacture of the two bio-batches. Dissolution profiles of the proposed 150 mg and 300 mg products have been compared in the same three media and dissolution conditions. The results indicate that the dissolution profiles are similar.
The dissolution characteristics were shown to be comparable to those of the reference product. The products used in the bioequivalence studies are acceptable.

Manufacturing process
The manufacturing process comprises wet granulation and subsequent compression of the lubricated blend into core tablets that include the active substance. The tablet cores are subsequently coated by the prolonged releasing ethyl cellulose coating, a gastro-resistant coating, and a hydrophilic film coating and finally imprinted. Adequate validation data have been provided of the three batches of both strengths of the intended batch scales.

Control of excipients
In-house specifications are applied for the excipients silica colloidal anhydrous, the Opadry coating and the Opacode imprinting ink. For the other excipients reference is made to the Ph.Eur. All specifications are acceptable.

Quality control of drug product
The drug product control comprises tests for description, identification, average mass, water content, dissolution, assay, uniformity of dosage units, related substances, solvents and microbial quality. The methods have been adequately validated. The ranges of the dissolution specifications are acceptable and in line with the Guideline on the quality of Modified Release products. An additional, two-step dissolution method will be introduced post approval.
Results of batch analysis have been provided of nine batches of both strengths, including the biobatches. All results comply with the proposed specifications.

Stability of drug product
Results of stability studies have been submitted of full-scale batches stored up to 18 months at normal conditions (25°C/60%RH) and up to 6 months at accelerated conditions (40°C/75%RH). All results comply. The only clear trend observed is a decrease in dissolution. Based on the currently available data, the products can be approved with the current dissolution method, with a shelf-life of 12 months and storage condition 'Do not store above 25°C. Store in the original packaging to protect from moisture and light'. Photostability should be re-evaluated when the new dissolution method is introduced.

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 150 mg and 300 mg, modified-release tablets have 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 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 multiple bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two single-dose studies under fasting conditions with the 300 and 150 mg tablets, one single study under fed conditions with the 300 mg tablets and one study under steady state conditions with the 300 mg tablets.

The pharmacokinetic profile of the test product Bupropion HCl Sandoz retard (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Elontril (GlaxoSmithKline GmbH, Germany).

After the first round of assessment two additional studies were submitted: a 150 mg single dose, fed study, and a 150 mg multiple dose study.

The choice of the reference product in the bioequivalence studies 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 in the bioequivalence studies have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used 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 42 healthy male subjects, aged 20 - 42 years. Each subject received a single dose (300 mg) of one of the 2 bupropion HCl formulations. The tablet was orally administered after an overnight fast of at least 10 hours with 240 ml water. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were taken just before dosing and at 1.0, 2.0, 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, 12, 16, 20, 24, 36, 48, 72, 96 and 120 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
One subject was withdrawn from the study as he did not reported for the second period. The remaining 41 subjects completed the study and were evaluated.

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

Treatment N=41	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2491 ± 567	2551 ± 572	227 ± 70.1	5.0 (4.0 - 9.0)	--
Reference	2248 ± 641	2306 ± 641	200 ± 54.7	4.5 (3.5 – 10)	--
***Ratio (90% CI)**	1.13 (1.05 - 1.22)	--	1.13 (1.05 - 1.22)	--	--
CV (%)	20.8	--	20.2	--	--

$AUC_{0-\infty}$ 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

**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 44 healthy male subjects, aged 19 - 41 years. Each subject received a single dose (300 mg) of one of the 2 bupropion HCl formulations. After an overnight fast of at least 10 hours a high-fat, high-calorie breakfast was served. The breakfast consisted two slices of bread, 2 eggs, chicken, potatoes and milk (1000 Kcal). The tablet was orally administered just after the subjects finished their breakfast. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were taken just before dosing and at 1.0, 2.0, 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, 12, 16, 20, 24, 36, 48, 72, 96 and 120 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 subject were withdrawn from the study: three did not report for the second period and one withdrew due to adverse events. Forty subjects were included in the analysis.

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

Treatment N=40	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2685 ± 609	2746 ± 614	235 ± 77.0	6.5 (4.5 - 10.0)	--
Reference	2668 ± 605	2733 ± 612	213 ± 46.0	5.75 (4.5 - 12.0)	--
***Ratio (90% CI)**	1.00 (0.95- 1.05)	--	1.06 (0.98 - 1.14)	--	--
CV (%)	12.9	--	20.2	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Study III – 150 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 50 healthy male subjects, aged 19-41 years. Each subject received a single dose (150 mg) of one of the 2 bupropion HCl formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were taken just before dosing and at 1.0, 2.0, 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, 12, 16, 20, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

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

Results
Forty-five subjects completed both treatments. Three subjects did not show up for the second treatment and 2 were withdrawn for medical reasons.

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

Treatment N=45	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	919 ± 313	964 ± 322	78.0 ± 35.9	5.5 (3.0 - 12.0)	--
Reference	879 ± 323	918 ± 334	71.9 ± 27.4	5.0 (3.5 - 12.0)	--
***Ratio (90% CI)**	1.05 (0.96 - 1.16)	--	1.05 (0.95 - 1.16)	--	--
CV (%)	28.1	--	29.5	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Study IV - 300 mg at steady state

Design

A multiple-dose, two-way, two sequence, two period crossover bioequivalence study was carried out in 44 healthy male subjects, aged 20-44 years. The subjects received the investigational drugs once daily on 8 consecutive days after an overnight fast of at least 10 hours with 240 ml of water.

Blood samples were taken just before dosing on each dosing day and after the last dose (dose 8) at 1.0, 2.0, 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, 12, 16, 20, 24 hours upon dosing. The wash-out period between the treatments was 14 days.

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

Results

Forty-two subjects completed both treatments. Two were withdrawn, one due to vomiting and one because he did not cooperate adequately.

Table 4. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)

Treatment N=42	AUC_{τ} ng/ml/h	$C_{max,ss}$ ng/ml	$C_{min,ss}$ ng/ml	t_{max} h
Test	2268 ± 632	238 ± 106	39.8 ± 13.0	5.0 (4.0 - 10.0)
Reference	2099 ± 577	208 ± 62.1	38.1 ± 15.1	4.5 (3.0 - 10.0)
***Ratio (90% CI)**	1.07 (1.02 - 1.13)	1.12 (1.03 - 1.21)	1.06 (0.98 - 1.14)	--
CV (%)	13.8	20.1	21.1	--

AUC_{τ} area under the plasma concentration-time curve over the dosing interval
$C_{max,ss}$ maximum plasma concentration
$C_{min,ss}$ minimum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Table 5. Secondary pharmacokinetic parameters of bupropion after oral administration in steady-state (non-transformed values; arithmetic mean ± SD; n=42)

Treatment	$C_{av,ss}$* ng/ml	Fluctuation %
Test	811 ± 366	57 ± 24
Reference	803 ± 418	51 ± 24

*$C_{av,ss}$ - Average plasma drug concentration during a dosing interval at steady-state

Conclusion on bioequivalence studies I-IV

Based on the submitted bioequivalence studies Bupropion HCl Sandoz retard 300 mg is considered bioequivalent with Elontril® 300 mg modified-release tablets. Under fasted and fed conditions the 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25.

The results at steady state show that the $AUC_{0-\tau}$ and $C_{min,ss}$ ratios are within the predefined acceptance criteria of 0.80 – 1.25. Also secondary variables are considered similar between both treatments.

Bioequivalence has been demonstrated for the 150 mg strength under fasted studies. Other studies with the 150 mg tablets (fed and steady-state) cannot be waived. The tablet cores are dose-proportional. However, the size and shape of both strengths needs to be evaluated for the proposed waiver under fed conditions. According to the SmPC the 150 mg tablets are round, biconvex and the 300 mg tablets biconvex. If proportional strengths have different size/shape, two strengths representing the most extreme difference should be tested for bioequivalence. Therefore, the MAH submitted results of additional studies under fed and steady state conditions.

Study V – 150 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 52 healthy male subjects, aged 18-45 years. Each subject received a single dose (150 mg) of one of the 2 bupropion HCl formulations. After an overnight fast of approximately 10 hours, volunteers were administered a high fat, high calorie breakfast (about 1000 calories). Dosing was done 30 minutes after the start of the breakfast.

A washout period of 14 days was maintained between the study periods. Blood samples were collected pre-dose (within 1.50 h prior to dosing) and at 1.00, 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 12.00, 16.00, 20.00, 24.00, 36.00, 48.00, 72.00, 96.00 and 120.00 hours after dosing in each study.

The sampling schedule is acceptable considering the absorption rate and the half-life of 20 hrs. The washout period is sufficient to avoid the carry-over. Also the quantity and composition of breakfast and the washout period are acceptable.

Results

In total, 6 subjects were withdrawn from the study. One subject was withdrawn from the study on medical safety grounds and due to vomiting at critical time as specified in the approved study protocol after period-1 dosing. Two subjects did not report to the clinical facility for period-2 check-in and another two subjects were found positive in breath alcohol test during period-2 check in. One subject was found positive in urine scan for drug of abuse test during period-2 check-in. Thus, 46 subjects who completed both study periods were included in the statistical analysis.

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median, range)) of bupropion after under fed conditions.

Treatment N=46	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	752.25	--	69.55	8.01 (4.5-12.0)	--
Reference	765.19	--	66.66	7.09 (4.5-16.0)	--
***Ratio (90% CI)**	0.98 (0.92-1.05)	--	1.04 (0.95-1.14)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	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				

**ln-transformed values*

Study VI - 150 mg at steady state

Design

A multiple-dose, two-way, two sequence, two period crossover bioequivalence study was carried out in 56 healthy male subjects, aged 18-45 years. The subjects received the investigational drugs once daily on 8 consecutive days after an overnight fast of at least 10 hours with 240 ml of water.
Blood samples were withdrawn within 5 minutes prior to Dose 1 of period 1, Dose 6 to 8 in each period and at 1.00, 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 12.00, 16.00, 20.00, 24.00 hours after dosing of Dose 8 in each period. No washout period was maintained between each treatment schedule.

The design of the bioequivalence study was acceptable. In this steady state study, the build-up period is sufficiently long (at least 5 times the terminal half-life), and the absence of a washout period is appropriate.
The pharmacokinetic parameters $C_{max,ss}$, $C_{t,ss}$ and AUC_{τ} were used to evaluate bioequivalence.

Results

Two subjects were withdrawn from the study on medical safety grounds on Day 1 and Day 2 of study period II. Fifty-four subjects were included in the statistics analysis.

Table 7. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean)

Treatment N=54	**AUC_{τ}** ng/ml/h	**$C_{max,ss}$** ng/ml	**$C_{t,ss}$** ng/ml	**t_{max}** h
Test	725.68	77.26	12.99	--
Reference	717.46	73.52	12.84	--
***Ratio (90% CI)**	1.01 (0.95-1.08)	1.05 (0.98-1.12)	1.01 (0.94-1.09)	--
CV (%)	--	--	--	--

AUC_{τ}	area under the plasma concentration-time curve over the dosing interval
$C_{max,ss}$	maximum plasma concentration
$C_{t,ss}$	trough concentrations at steady state
t_{max}	time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence studies V-VI

Based on the two additional bioequivalence studies, it can be concluded that Bupropion HCl Sandoz retard 150 mg is considered bioequivalent with Elontril® 150 mg modified-release tablets. Under fed conditions the 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Also the results at steady state show that the $C_{max,ss}$, $C_{t,ss}$, AUC_{τ} ratios are within 0.80–1.25. Herewith bioequivalence has been demonstrated for the 150 mg modified-release tablet at fed and steady state, as well as fasted state (study III).

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 Sandoz retard 150 mg and 300 mg, modified-release tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity Seizures or seizure disorder Suicide/suicidal thoughts or clinical worsening Increased blood pressure Drug interactions
Important potential risks	Arrhythmias and conduction disorders Pregnancies Medication errors Increased ocular pressure Withdrawal effects Abuse potential
Missing information	Use in children or adolescents aged less than 18 years

The MAH committed to the risk minimisation measures of the innovator product, which means that the company should have an education communication plan available. The additional risk minimisation measures for the safety concern “medication errors” are laid down in the RMP.
The MAH should compile and submit this educational material, the final version of which should be agreed upon by the national competent authority, before marketing of the product in each member state.

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

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. From the results it was concluded that the Bupropion Sandoz PL fulfils the readability guideline text, layout and design recommendations and complies with the European Commission’s recommendations which state that patients shall easily locate, comprehend and appropriately act upon the information conveyed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bupropion HCl Sandoz retard 150 mg and 300 mg, modified-release tablets have a proven chemical-pharmaceutical quality and are generic forms of Elontril 150 mg and 300 mg modified-release. 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. Studies demonstrated bioequivalence for both strengths under all three conditions required: single dose fasted, single dose fed conditions and at steady state.

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 150 mg and 300 mg, modified-release tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 March 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Removal of the imprint of the 150 mg tablet.	NL/H/3042/ 001-002/IA/ 001	IA	31-7-2015	30-8-2015	Approval	No