LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bupropion SUN
(bupropion hydrochloride)

SE/H/2459/01-02/DC

This module reflects the scientific discussion for the approval of Bupropion SUN. The procedure was finalised on 2024-10-02. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bupropion SUN, 300 mg, 150 mg, Modified-release tablet.

The active substance is bupropion hydrochloride, bupropion. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Bupropion SUN, 150 mg and 300 mg Modified-release tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, ES, IT, NL, PL and RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Wellbutrin XR, modified-release tablet, 150 mg authorised in NL since 2007, with GlaxoSmithKline BV as marketing authorisation holder.

The reference product used in the bioequivalence study is Elontril, modified-release tablet, 150 mg and 300 mg from DE with Glaxo Wellcome S.A as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of bupropion hydrochloride are well known. As bupropion hydrochloride is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Bupropion SUN is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Bupropion SUN from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted 7 bioequivalence studies comparing Bupropion SUN with the reference product Elontril.

Pharmacokinetic properties of the active substance
Absorption: The absolute bioavailability of bupropion is not known; urinary excretion data, however, show that at least 87% of the dose of bupropion is absorbed. Following an oral dose of bupropion modified release tablets maximal plasma concentrations occur at approximately 5 hours.

The pharmacokinetics of bupropion modified release is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The AUC and Cmax values of bupropion and its active metabolites hydroxybupropion and threohydrobupropion increase dose proportionally over a dose range of 50-200 mg following single doses and over a dose range of 300-450 mg/day following chronic dosing.

Elimination: The elimination half-life of hydroxybupropion is approximately 20 hours. The elimination half-lives for threohydrobupropion and erythrohydrobupropion are longer (37 and 33 hours, respectively) and steady-state AUC values are 8 and 1.6 times higher than that of bupropion, respectively. Steady-state for bupropion and its metabolites is reached within 8 days.

Study BUPRO-10-21 (single-dose, 150 mg fed)
Methods
This was a single-dose, two-way crossover study conducted in 72 healthy volunteers, comparing Bupropion Sun 150 mg, modified release tablet with Elontril, 150 mg, modified release tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 96 hours post-dose. Plasma concentrations of bupropion were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 7th October 2022 and 16th November 2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for bupropion

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test n=60	**958.88 ± 270.75**	**1016.96 ± 287.05**	**96.42 ± 34.82**	**8.25 (3.00-9.50)**
Reference n=61	**984.47 ± 274.93**	**1041.71 ± 289.21**	**99.71 ± 25.58**	**7.00 (3.00-9.50)**
Ratio (90% CI) n=55*	**97.68 (93.59-101.96)**	**97.76 (93.74-101.96)**	**94.67 (87.71-102.17)**	**_____**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
***completed both study periods*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study BUPRO-09-21 (Initial single-dose study, 150 mg fasting)

Methods

This was a single-dose, two-way crossover study conducted in 72 healthy volunteers, comparing Bupropion Sun 150 mg, modified release tablet with Elontril, 150 mg, modified release tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 96 hours post-dose. Plasma concentrations of bupropion were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 9th September 2022 and 5th October 2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for bupropion, n= 60

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test n=62	**840.47±223.57**	**892.12±237.35**	**103.94±37.02**	**4.50(2.00-6.50)**
Reference n=63	**845.76±244.59**	**901.06±263.28**	**89.82±30.23**	**4.50(3.00-6.50)**
Ratio (90% CI) n=60*	**101.05 (97.03–105.23)**	**100.85 (96.92-104.94)**	**117.36 (109.80 –125.45)**	**_____**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
***completed both study periods*

For $AUC_{0-\infty}$ and $AUC_{0-\infty}$ the 90% confidence interval for the ratio of the test and reference products

were within the conventional acceptance range of 80.00-125.00%.
However, for C_{max} the 90% confidence interval for the ratio of the test and reference products fell outside (upper limit **125.45**) the conventional acceptance range of 80.00-125.00%.

Study BUPRO-15-22 (repeated single-dose study, 150 mg fasting)
Methods
This was a single-dose, two-way crossover study conducted in 112 healthy volunteers, comparing Bupropion Sun 150 mg, modified release tablet with Elontril, 150 mg, modified release tablet under fasted conditions. Blood samples for concentration analysis were collected pre-dose and up to 96 hours post-dose. Plasma concentrations of bupropion were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 16th June 2023 and 5th July 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 3 below.

Table 3 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for bupropion

Treatment	**AUC_{0-t}** ng*h/ml	**$AUC_{0-\infty}$** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test n=102	**783.09±223.84**	**839.53±239.41**	**88.52±28.09**	**4.50(2.50-70)**
Reference n=102	**799.680 ± 224.20**	**854.26 ± 242.44**	**83.36 ±25.09**	**4.50(2.50-6.50)**
Ratio (90% CI) n=98*	**97.80 (94.65 – 101.05)**	**98.06 (95.03-101.20)**	**106.76 (101.43-112.37)**	**_____**

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*
***completed both study periods*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for bupropion in the repeated study.

Pooled analysis (single-dose study, 150 mg fasting)
Two single-dose fasting studies with the 150 mg strength were performed as the initial study did not demonstrate BE for Cmax. An exploratory analysis was done by pooling data of both studies. The results from the pooled analysis of study BUPRO-09-21 and study BUPRO-15-22 are presented in Table 4 below.

Table 4 Ratio, 90% CI and 95% CI in the pooled analysis of combined two studies (BUPRO-09-21 and BUPRO-15-22), n =158

	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
Ratio (90% CI)	**98.97 (96.51-101.50)**	**99.07 (96.68-101.52)**	**110.46 (106.05-115.04)**
Ratio (95% CI)	**98.97 (96.04-102.00)**	**99.07 (96.23-102.00)**	**110.46 (102.22-115.95)**
Intra Subject CV (%)	**22.08**	**13.61**	**13.15**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration			

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% and 95% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for bupropion in the repeated study.

Study BE/22/190 (Multiple dose, 150 mg fasting)

Methods

This was a multiple-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Bupropion Sun 150 mg, modified release tablet with Elontril, 150 mg, modified release tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose on day 1 to day 7 and up to 24.0 hours post-dose after drug administration of day 7. Plasma concentrations of bupropion were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-\tau(ss)}$, $C_{max(ss)}$ and $C_{trough(ss)}$. The study was conducted between 8th October 2022 and 14th October 2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 5 below.

Table 5. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Bupropion, n=31.

Treatment	**$AUC_{0-\tau}$** **ng*h/ml**	**C_{max}** **ng/ml**	**C_{trough}** **ng/ml**	**t_{max}** **h**
Test	**942.64 ± 238.07**	**106.62 ± 31.40**	**15.54 ± 5.14**	**4.67 (3.50-70)**
Reference	**952.42 ± 217.40**	**101.70 ± 27.87**	**15.82 ± 4.78**	**5.00 (3.00-8.50)**
***Ratio (90% CI)**	**98.42 (92.80-104.38)**	**104.07 (95.49-113.42)**	**97.93 (91.02 -105.36)**	**_____**
$AUC_{0-\tau}$ area under the plasma concentration-time curve during one dosing interval C_{max} maximum plasma concentration C_{trough} plasma concentration at the end of the dosing interval t_{max} time for maximum plasma concentration				

**calculated based on ln-transformed data*

For $AUC_{0-\tau}$, C_{trough} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study BUPRO-12-21 (single-dose, 300 mg fed)

Methods

This was a single-dose, two-way crossover study conducted in 72 healthy volunteers, comparing Bupropion Sun 300 mg, modified release tablet with Elontril, 300 mg, modified release tablet under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 96 hours post-dose. Plasma concentrations of bupropion were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and

C_{max}. The study was conducted between 13th May 2022 and 8th June 2022.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 6 below.

Table 6 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for bupropion

Treatment	**AUC_{0-t}** ng*h/ml	**$AUC_{0-\infty}$** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test n=54	**1864.14 ± 529.63**	**1964.88 ± 565.38**	**156.73 ± 47.58**	**8.50 (2.00 - 13.00)**
Reference n=58	**1979.98 ± 584.91**	**2096.00 ± 642.19**	**181.03 ± 56.56**	**8.25 (3.00 - 9.50)**
Ratio (90% CI) n=50*	**97.33 (93.03 - 101.82)**	**97.11 (93.02 - 101.38)**	**89.78 (82.76 - 97.40)**	**_____**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*
*** completed both study periods*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study BUPRO-11-21 (single-dose study, 300 mg fasting)
Methods
This was a single-dose, two-way crossover study conducted in 72 healthy volunteers, comparing Bupropion Sun 300 mg, modified release tablet with Elontril, 300 mg, modified release tablet under fasted conditions. Blood samples for concentration analysis were collected pre-dose and up to 96 hours post-dose. Plasma concentrations of bupropion were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 8th April 2022 and 11th May 2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 7 below.

Table 7 Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for bupropion

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test n=64	**1498.47 ± 426.19**	**1563.78 ± 439.56**	**164.33 ± 52.07**	**4.50 (2.50-7.00)**
Reference n=62	**1509.38 ± 357.22**	**1579.55 ± 381.26**	**164.24 ± 55.65**	**4.50 (2.50-7.00)**
***Ratio (90% CI) n=59**	**97.50 (93.23-101.96)**	**97.59 (93.51-101.84)**	**99.05 (92.74-105.79)**	**_____**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration				

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study BE/22/191 (Multiple dose, 300 mg fasting)

Methods

This was a multiple-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Bupropion Sun 300 mg, modified release tablet with Elontril, 300 mg, modified release tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose on day 1 to day 7 and up to 24.0 hours post-dose after drug administration of day 7. Plasma concentrations of bupropion were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0-\tau(ss)}$, $C_{max(ss)}$ and $C_{trough(ss)}$. The study was conducted between 27th September 2022 and 7th November 2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 8 below.

Table 8. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for Bupropion, n=30.

Treatment	$AUC_{0-\tau}$ ng*h/ml	C_{max} ng/ml	C_{trough} ng/ml	t_{max} h
Test	**1662.12 ± 339.60**	**155.53 ± 33.62**	**31.41 ± 7.95**	**5.17 (4.33 - 10.00)**
Reference	**1677.99 ± 277.67**	**168.20 ± 48.49**	**30.15 ± 5.70**	**4.67 (4.00 - 9.00)**
***Ratio (90% CI)**	**98.41 (93.41 - 103.68)**	**93.74 (86.73 - 101.31)**	**102.88 (96.35 - 109.86)**	-
$AUC_{0-\tau}$ area under the plasma concentration-time curve during one dosing interval C_{max} maximum plasma concentration C_{trough} plasma concentration at the end of the dosing interval t_{max} time for maximum plasma concentration				

**calculated based on ln-transformed data*

For $AUC_{0-\tau}$, C_{trough} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) and Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1). The bioanalytical methods were adequately validated. A complete study package with single-dose fed, single-dose fasting, and multiple-dose fasting has been submitted for both strengths, which is acceptable for this prolonged-release formulation. For the 150 mg strength, two single dose fasted studies were performed as the initial study did not demonstrate bioequivalence for C_{max} as discussed below.

In all studies except the initial single-dose fasted study with the 150 mg strength (BUPRO-09-21), the 90% confidence intervals for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for bupropion for all primary PK parameters.

In study BUPRO-09-21, for C_{max} the 90% confidence interval for the ratio of the test and reference products fell outside (upper limit 125.45) the conventional acceptance range of 80.00-125.00%. In the repeat fasted study with the 150 mg strength, results were within acceptance criteria. The pharmacokinetic analysis on the initial study was based on 60 subjects while the repeat study ((BUPRO-10-21) was conducted on a larger sample size, 98 subjects.

According to the bioequivalence guideline, if for a particular formulation at a particular strength multiple studies have been performed some of which demonstrate bioequivalence and some of which do not, the body of evidence must be considered as a whole. The results of the pooled analysis were within acceptance criteria using 90% CI as well as using 95% CI. The fact that the repeat study was conducted on a larger sample size together with the results of the pooled analysis are considered sufficient in order to conclude bioequivalence for the 150 mg strength in the fasted state.

Based on the submitted bioequivalence studies, Bupropion Hydrochloride is considered bioequivalent with Elontril.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 SUN.

Part II Safety specification

The MAH has submitted the version 0.2 RMP dated 2024-02-07 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Assessor's comment: The Applicant have updated the summary of safety concerns and is now in line with the HaRP assessment report for bupropion hydrochloride. Issue resolved.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
Issue is resolved.

The submitted Risk Management Plan, version 0.2 signed 2024-02-07 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PL was English.

The results show that the package leaflet 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

The quality of the generic product, Bupropion SUN, is found adequate. There are no objections to approval of Bupropion SUN, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Bupropion SUN, 300 mg, 150 mg, Modified-release tablet was positively finalised on 2024-10-02.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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