LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bupropion Bluefish
(bupropion hydrochloride)

SE/H/2013/02/DC

This module reflects the scientific discussion for the approval of Bupropion Bluefish. The procedure was finalised on 2022-06-30. 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 Bluefish, 150 mg, modified-release tablet.

The active substance is bupropion hydrochloride. 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 is an extension, new strength, of the previously authorised product: Bupropion Bluefish, 300 mg, modified-release tablet.

The application for Bupropion Bluefish, 150 mg, modified-release tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Bluefish Pharmaceuticals AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS).

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

The reference product used in the bioequivalence study is Elontril, 150 mg, modified-release tablet from Germany with GlaxoSmithKline GmbH & Co. as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since product name 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 Bluefish from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted 3 bioequivalence study(ies) comparing Bupropion Bluefish 150 mg modified release (MR) tablets with the reference product Elontril 150 mg MR tablets.

Pharmacokinetic properties of the active substance

Absorption: The absolute oral bioavailability of bupropion is not known, but urinary excretion data show that at least 87% of the dose 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 pharmacokinetics of bupropion is linear within the dose range 50-200 mg following single dose and 300-450 mg/day following repeated doses.

Elimination: The terminal half-life is approximately 20 hours. Steady-state for bupropion and its metabolites is reached within 8 days.

Study 0331-19 (single dose fasting)
Methods
This was a single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Bupropion Bluefish, 150 mg, MR-tablets with Elontril, 150 mg, MR-tablets 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 LC/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 09 January 2020 – 28 January 2020.

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, t_{max} median, range) for substance, n=28.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	815.160 ± 297.7383	859.058 ± 307.6340	68.856 ± 24.2531	7.500 (4.000 - 14.000)
Reference	754.152 ± 320.7769	792.878 ± 329.3051	65.812 ± 29.6729	5.000 (2.500 - 7.500)
***Ratio (90% CI)**	**110.9 (98.65-124.71**	**110.8 (98.24-124.99)**	**108.4 (94.41-124.41)**	**-**

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 0260-20 (single dose fed)

Methods

This was a single-dose, two-way crossover study conducted in 80 healthy volunteers, comparing Bupropion Bluefish, 150 mg, MR-tablets with Elontril, 150 mg, MR-tablets 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 LC/MS/MS method. Samples were stored within validated conditions. 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 21 November 2020 – 16 December 2020.

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=76.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	811.103 ± 217.3990	852.298 ± 224.0479	78.458 ± 21.2603	5.500 (3.000 - 10.000)
Reference	761.283± 254.9090	799.470 ± 260.2180	81.066 ± 27.1450	6.000 (2.000 – 10.000)
***Ratio (90% CI)**	**107.8(102.79-113.16**	**107.8 (102.90-112.94)**	**98.4 (92.53-104.58)**	**-**

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 0333-19 (multiple dose fasting)

Methods

The study was a randomised, two-treatment, two-period, two-sequence multiple-dose full replicate study conducted in 32 healthy volunteers under fasting conditions. From Day 01 to Day 11, after an overnight fast of at least 10 hours, Bupropion Bluefish, 150 mg, MR-tablets or Elontril, 150 mg, MR-tablets was administered. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of bupropion were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for Cτ,ss, Cmax,ss and AUC0-τ,ss. The study was conducted between10 February 2020 – 23 March 2020.

Results

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

Table 2. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for bupropion, n=28.

Treatment	$AUC_{0-\tau}$ ng*h/ml	C_{max} ng/ml	Cτ,ss ng/ml	t_{max} h
Test	902.671 ± 300.5458	94.132 ± 36.6194	13.615 ± 5.2542	5.000 (3.000 - 12.000)
Reference	912.316 ± 296.1959	94.875 ± 30.7709	14.599 ± 5.6201	5.000 (3.000 - 10.000)
***Ratio (90% CI)**	**98.8 (93.91 - 103.97)**	**97.6 (87.37 - 99.44**	**93.2 (91.24 - 104.37**)	-

$AUC_{0-\tau}$	area under the plasma concentration-time curve during one dosing interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
t_{max}	time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC0-τ , Cτ,ss and Cmax 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.

Discussion and overall conclusion

The bioequivalence studies and the 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/Corr). The bioanalytical methods were adequately validated. In study 0260-20 samples were stored outside the validated temperature range for long term storage, however the validated bench-top storage conditions covered the actual storage conditions of the clinical samples and no concern is raised.

The mean ratios of all the primary pharmacokinetic parameters between the test products and reference products in the two single dose as well as in the steady-state studies met the required ratios of 80 -125%.

Based on the submitted bioequivalence studies, Bupropion Bluefish 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 Bluefish.

Safety specification

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Seizures • 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

Pharmacovigilance Plan

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

Risk minimisation measures

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

Summary of the RMP
The submitted Risk Management Plan, version 2.0 signed 13 July 2021 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

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:

Content
Elontril, modified release tablets, 150 mg and 300 mg, NL/H/786/01-02/DC

Layout
Venlafaxine, capsules, 37.5mg, 75mg and 150mg, SE/H/1870/01-03/DC (previously UK/H/1400/01-03/DC)

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Bupropion Bluefish, is found adequate. There are no objections to approval of Bupropion Bluefish, from a quality, non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. 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 Bluefish, 150 mg, modified-release tablet was positively finalised on 2022-06-30.

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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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