COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Libroxar 2 mg/0.5 mg and 8 mg/2 mg sublingual tablet

(buprenorphine hydrochloride/naloxone hydrochloride dihydrate)

NL/H/4400/001-002/DC

Date: 31 October 2019

This module reflects the scientific discussion for the approval of Libroxar 2 mg/0.5 mg and 8 mg/2 mg sublingual tablet The procedure was finalised on 18 August 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

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
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 Libroxar 2 mg/0.5 mg and 8 mg/2 mg sublingual tablet from Laboratoires SMB S.A.

The product is indicated for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse.
Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

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 Suboxone 2 mg/0.5 mg and 8 mg/2 mg, sublingual tablets (EU/1/06/359/001-006), which has been registered via a centralised procedure by Indivior Europe Limited since 26 September 2006.

The concerned member states (CMS) involved in this procedure were Belgium, Cyprus, Czech republic, Denmark, Finland, Germany, Greece, Luxembourg, Norway, Portugal, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Libroxar 2 mg/0.5 mg is an off-white to brownish hexagonal biconvex tablet embossed with “N2” on one side. Each tablet contains buprenorphine hydrochloride equivalent to 2 mg buprenorphine and naloxone hydrochloride dehydrate equivalent to 0.5 mg naloxone

Libroxar 8 mg/2 mg is an off-white to brownish hexagonal biconvex tablet embossed with “N8” on one side. Each tablet contains buprenorphine hydrochloride equivalent to 8 mg buprenorphine and naloxone hydrochloride dehydrate equivalent to 2 mg naloxone

The sublingual tablets are packed in OPA/Al/PVC-Al blisters.

The excipients are: lactose monohydrate, mannitol, povidone, maize starch, citric acid, sodium citrate, ascorbic acid, disodium edetate, acesulfame K (E950), lemon flavor, magnesium stearate.

The two tablet strengths are dose proportional.

II.2 Drug Substances

The active substances are buprenorphine hydrochloride and naloxone hydrochloride dihydrate are both established active substances described in the European Pharmacopoeia. Both are white or almost white crystalline powders and contain several chiral centres. Buprenorphine hydrochloride is sparingly soluble in water, while naloxone hydrochloride dihydrate is freely soluble in water. No polymorphism of both active substances has been reported.

The CEP procedure is used for both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substances
The active substance specification of both active substances is in line with the Ph. Eur. and the CEP, supplemented with a test for particle size distribution. Batch analytical data demonstrating compliance with the drug substance specifications have been provided for three batches by the drug substance manufacturers as well as the drug product manufacturer.

Stability of drug substances
Both active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 composition and manufacturing process of the drug products have been optimised on lab-scale batches. While the optimised composition of the lab-scale

batches is the same as the composition of the commercial-scale batches, differences are observed between the optimised manufacturing process at lab-scale and the manufacturing process of commercial-scale batches. This has been explained. The discriminatory power of the proposed dissolution method has been demonstrated up to time point 7.5 minutes.
A bioequivalence study was performed with the highest product strength of the test and reference product. For the lower product strength a biowaiver is acceptable, based on comparable *in vitro* dissolution data between the biobatch and the additional strength. Comparative *in vitro* dissolution results between the drug product and reference product have be provided supplementary to the bioequivalence study.

Manufacturing process
The drug products are manufactured by wet granulation, blending and lubrication and compression. The product is manufactured using conventional manufacturing techniques. Both strengths are prepared from the same blend. Due to the low drug load, the manufacturing process is considered a non-standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot batches of each strength.

Control of excipients
The excipients comply with the Ph. Eur. or in-house (lemon flavour) requirements. These specifications are acceptable. The use and amount of the antioxidants ascorbic acid and EDTA as well as the combination have been adequately justified.

Quality control of drug product
The product specification includes tests for description, assay of ascorbic acid, assay of disodium edetate, disintegration, loss on drying, hardness, friability and microbial limits. Furthermore, for each active substance the following tests are included: two identification tests, assay, related substances, dissolution and uniformity of dosage units. Except for the assay of ascorbic acid, the release and shelf-life limits of all tests are the identical. Microbial quality and uniformity of dosage units during shelf-life are tested periodically. The specification is acceptable.
The proposed dissolution limits for both drug substances (Q=85% at 7.5 min) are based on the dissolution of the biobatch. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on the three pilot batches of each strength, demonstrating compliance with the proposed release specification.

Stability of drug product
Stability data on the product have been provided for three pilot batches of the 2 mg/0.5 mg drug product and three pilot batches plus the biobatch of the 8 mg/2 mg drug product. The batches were stored at 25°C/60% RH (biobatch 24 months, other batches 18 months) and 30°/65% RH (24 months for batch R734/B (8/2 mg strength); 12 months for all other batches) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the guidance on stability. The batches were stored in the commercial packaging.

After storage for 6 months at 40ºC, a significant change in appearance was observed. At 30°C and 25°C, no changes in appearance were observed and all other tests complied with the proposed shelf-life limits.
Based on the available stability data, a shelf life of 2 years has been granted with the storage condition "Do not store above 30°C". Based on the photostability study results, the drug product should be stored in the blister in order to protect from light and moisture.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate, obtained from bovine milk, is used as excipient in the drug product. A statement from the supplier of lactose monohydrate is provided, which describes that the BSE risk of the material is negligible.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Libroxar 2 mg/0.5 mg and 8 mg/2 mg sublingual tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Libroxar 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 Suboxone, 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

Buprenorphine hydrochloride and naloxone hydrochloride dihydrate are well-known active substances 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Libroxar 8 mg/2 mg (Laboratoires SMB S.A., Belgium) is compared with the pharmacokinetic profile of the reference product Suboxone 8 mg/2 mg sublingual tablets (Indivior Europe Limited, Ireland).

The choice of the reference product in the bioequivalence study is justified, as it has been authorised through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The bioequivalence study has been performed with the highest strength of the test product. The MAH applied for a biowaiver for the additional 2 mg/0.5 mg strength. The two different strengths are prepared from the same common blend. Moreover, the different strengths are manufactured by the same process, have the same qualitative composition and are quantitatively proportional in accordance with requirement a), b) and c) of the general biowaiver criteria from CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. Adequate comparative *in vitro* dissolution results have been provided. A biowaiver has been granted.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 71 healthy opioid non-dependent subjects (54 males/17 females), aged 18-55 years. Each subject received a single dose (8 mg/2 mg) of one of the 2 buprenorphine/naloxone formulations. After an overnight fast, the tablets were administered in solid form, placed under the tongue until complete dissolution. No water was administered. For safety reasons, the volunteers took a medication (naltrexone 50 mg) the day before and just before the administration of the sublingual tablets, to decrease the risk of opioid-related adverse events. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout

period of 14 days.

Blood samples were taken pre-dose and at 10, 20, 30, 40, and 50 minutes and at 1, 1.25, 1.5, 1.45, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Seventy-two subjects were included in the study. One subject was withdrawn before dosing. A total of 10 subjects did not complete both periods; 9 due to withdrawal of their consent and 1 was withdrawn due to an adverse event. Sixty-two subjects completed the study entirely.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of buprenorphine under fasted conditions.

Treatment	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test N=66	25596 ± 7836	29019 ± 9475	3327 ± 965	1.0 (0.5 – 2.5)	25 ± 13
Reference N=65	27768 ± 8586	32035 ± 11139	3683 ± 1522	1.0 (0.5 - 3.0)	30 ± 30
***Ratio (90% CI)**	0.96 (0.89-1.03)	--	0.94 (0.88-1.01)	--	--
CV (%)	23	--	9	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of naloxone under fasted conditions.

Treatment	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test N=66	399 ± 159	418 ± 166	189 ± 76	0.5 (0.17 – 1.0)	3.9 ± 3.5

Reference N=65	426 ± 204	449 ± 211	211 ± 111	0.5 (0.33 - 0.83)	4.6 ± 4.8
***Ratio (90% CI)**	0.96 (0.89 - 1.05)	--	0.94 (0.85 - 1.03)	--	--
CV (%)	23	--	9	--	--

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study, Libroxar is considered bioequivalent with Suboxone.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Safety

A total of 45 treatment emergent adverse events (TEAEs) were reported during the study. Seventeen of them were reported by 13 subjects treated with Suboxone 8/2 mg and 28 were reported by 12 subjects treated with Libroxar 8/2 mg. All of them were considered of mild intensity.

Forty-three treatment-emergent adverse events were considered as related to the study drugs, 16 of them to Suboxone 8/2 mg and 27 to Libroxar 8/2 mg.

No serious adverse events and no adverse events of severe intensity have been reported with any of the two treatments. No patient was withdrawn due to an adverse event after administration of any investigational medicinal product.

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 Libroxar.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Fatal overdose o severe respiratory failure (mechanism for death by overdose)

	o use in patients with alcoholism/delirium tremens • Misuse and/or abuse (injection/intranasal/ pediatric use) • Hepatitis, hepatic events, use in patients with hepatic failure • Dependence • Drug withdrawal syndrome • Use during pregnancy and lactation (effects on newborn and infant) • CNS depression (effects on driving ability) • Allergic reactions
Important potential risks	• Use in patients with head injury and intracranial pressure • Peripheral oedema
Missing information	• Elderly patients >65 years old • Children <15 years old

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 Suboxone. 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

Libroxar 2 mg/0.5 mg and 8 mg/2 mg sublingual tablets have a proven chemical-pharmaceutical quality and are a generic form of Suboxone 2 mg/0.5 mg and 8 mg/2 mg, sublingual tablets. Suboxone 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 Libroxar with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 August 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