IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Bulexin 8 mg/2 mg sublingual tablets
Buprenorphine hydrochloride
Naloxone hydrochloride dihydrate
PA0281/267/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for "*Nalopren 2 mg/0,5 mg Sublingualtabletten*", "*Nalopren 4 mg/1 mg Sublingualtabletten*" and "*Nalopren 8 mg/2 mg Sublingualtabletten*" with the following indication:
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.
is approved.

EXECUTIVE SUMMARY

Problem statement

This decentralised application concerns a generic version of buprenorphine HCl and naloxone HCl, under the trade name Bupronox 2/0.5 mg, 4/1 mg and 8/2 mg SL tablets. In this Overview, the name Buprenorphine/Naloxone Pinewood is used.

The Applicant Pinewood Laboratories Ltd Ireland applied for a generic product of the European Reference product Suboxone® 2 mg/0.5 mg and 8 mg/2 mg sublingual tablets registered and marketed by Indivior UK Limited in European countries. The generic Bup/Nal SL tablets, subject of the present marketing authorisation application (MAA), were originally developed by GL Pharma.

The MAA was submitted according to Article 10(1)-Generic application of directive 2001/83/EC as amended.

The marketing authorization of the European reference product Suboxone® was granted through centralized procedure EMEA/H/C/000697 on 26 September 2006 for the 8 mg/2 mg and 2 mg/0.5 mg strengths.

With Germany as the Reference Member State in this Decentralized Procedure, Pinewood Laboratories Ltd applied for the Marketing Authorisations for Buprenorphine/Naloxone 2/0.5 mg, 4/1 mg and 8/2 mg SL tablets in Ireland.

The clinical data package including the BE study was assessed within the scope of preceding procedures DE/H/5111, 5112, 5113, 5117/01-03/DC including AT, CZ, DK, ET, FI, FR, HR, LV, LT, NL, SE, SI and UK as concerned member states. The preceding procedures were submitted by G.L. Pharma GmbH, Austria.

About the product

Buprenorphine is a semisynthetic opioid derived from thebaine that acts as a partial μ-opioid receptor agonist, and as an antagonist at the κ-opioid receptor. The binding affinity of BUP at both receptors is high (1000-fold higher than morphine) and dissociation from receptors is slow compared with other opioid analgesics.

The high binding affinity of BUP for the μ-opioid receptor and its slow dissociation contribute to its long duration of action [Mégarbane et al., 2006]. Agonist effects at μ-opioid receptors lead to euphoria, sedation, constipation, analgesia and respiratory depression. However being a partial agonist, BUP has maximal opioid effects lower than those of full agonists ('ceiling effect') providing a safety margin [Walsh et al., 1994; Ciraulo et al., 2006].

The analgesic potency of BUP is 25- to 50-fold higher than morphine at low doses (<0.8 mg) [Jasinski et al., 1978].

Naloxone HCl is a semisynthetic opioid antagonist without any agonist properties. Naloxone exerts little or no pharmacological effect when administered at usual doses to patients who have not recently received opioids. But in patients who have received large doses of opioids (e.g. drugs addicts), naloxone antagonizes effect of opioids and precipitates withdrawal. Due to its shorter duration of action, the effects of the opioid may return when the effect of naloxone dissipates [EPAR Suboxone®].

Effect of naloxone is dependent of the route of administration. After sublingual administration of Bup/Nal, the absorption of naloxone is minimal and the opioid agonist effect of BUP predominates. However, when the Bup/Nal tablets are crushed and injected, naloxone antagonizes the opioid agonist effect of BUP and would precipitate withdrawal [Orman et al, 2009]. The

addition of naloxone to BUP may thus decrease the abuse liability of BUP to be injected [Mendelson et al., 2003; Mendelson et al., 1996].

The proposed indication is fully in line with the originator and concerns the 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.

General comments on the submitted dossier

The present generic MAA is based on demonstration of bioequivalence of the three dose strengths of the test product, Buprenorphine/Naloxone G.L. (Pinewood) SL tablets, with the reference Suboxone® SL tablets.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a declaration is provided from the manufacturers responsible for manufacture of the finished product and batch release.

GLP/GCP
The clinical part of the study was conducted at the Debrecen University in Hungary, bioanalysis was undertaken at the ACC labs in Germany. Both sites were inspected by varying EU Inspectorates.

Name of the product	Bulexin 8 mg/2 mg sublingual tablets
Name(s) of the active substance(s) (INN)	Buprenorphine hydrochloride Naloxone hydrochloride dihydrate
Pharmacotherapeutic classification (ATC Code)	N07BC51
Pharmaceutical form and strength(s)	8 mg/2 mg sublingual tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/267/003
Marketing Authorisation Holder	Pinewood Laboratories Ltd Ballymacarbry Clonmel Co. Tipperary Ireland
MRP/DCP No.	IE/H/1386/003
Reference Member State	IE
Concerned Member State(s)	None

II. QUALITY ASPECTS

II.1 Quality aspects

Drug substance
The active substances Buprenorphine and Naloxone hydrochloride dihydrate are described in the European Pharmacopoeia (Ph. Eur.).

The active substances buprenorphine hydrochloride and naloxone hydrochloride dihydrate are monographed in the Ph. Eur. and each of them are supplied from two manufacturers. All manufacturers have a certificate of suitability issued by EDQM.

Drug Product

The aim of development was to obtain a medicinal product being similar to the reference product Suboxone® of the marketing authorization holder Indivior UK Limited. The sublingual tablets containing the active pharmaceutical ingredients buprenorphine and naloxone are available in two different dosage strengths: 2 mg / 0.5 mg and 8 mg / 2 mg. These two strengths and an additional strength, 4 mg / 1 mg, were objective of development.

The dissolution method has been sufficiently developed and its discriminatory power has been established for the respective tablet.

Dissolution profiles of the reference and the test products of all strengths have been presented, the dissolution profiles are comparable.

The Buprenorphine HCl / Naloxone HCl PR Tabletsare manufactured by blending of the active substances and the excipients and compressing into tablets.

The ingredients and the manufacturing process of the drug are considered suitable to produce a pharmaceutical product of the proposed quality.

All relevant quality characteristics of the drug substance and the drug product (release and shelf-life) are specified. The specification limits are derived from the available batch release and stability study data. The description of the analytical methods used to analyse the drug product are adequate, the validation results are plausible.

The proposed packaging material is characterised, supported by data and child resistency is confirmed.

The claimed shelf life of 36 months for the products in the applied strengths along with the storage recommendation „Do not store above 30°C" is justified by data.

III. NON-CLINICAL ASPECTS

Applications for Marketing Authorization of Buprenorphine/Naloxone 2/0.5 mg and 8/2 mg sublingual tablets are generic applications. As for Buprenorphine/Naloxone 4/1 mg sublingual tablets no reference medicinal product is available, the application for this strength is a hybrid application.

Pharmacodynamic, pharmacokinetic and toxicological properties of buprenorphine hydrochloride and naloxone hydrochloride dihydrate are well known. As buprenorphine hydrochloride and naloxone hydrochloride dihydrate are a widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The pharmacological and toxicological properties of buprenorphine and naloxone are well known and have been adequately summarised based on publicly available information in the Non-Clinical Overview.

The non-clinical overview is dated 1 March 2016 (Release Date) and has been updated (16 December 2020) with a discussion of the excipients used, as well as the impurities. The report refers 65 publications up to year 2016.
The non-clinical sections of the SmPC are consistent with the reference SmPC and therefore acceptable.

Environmental Risk Assessment (ERA)
Since Nalopren Sublingual Tablets 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.

IV. CLINICAL ASPECTS

Pharmacokinetics
The Applicant has submitted one bioequivalence study comparing the highest test SL tablet strength (8/2 mg) with the reference under single dose fasting conditions in support of the MAA for the three test product 2/0.5 mg, 4/1 mg and 8/2 mg formulations.

The three dose strengths of the test SL tablet formulation are qualitatively identical and quantitatively proportional. Based on the dose proportional composition of the test tablet strengths, the data obtained for the 8/2 mg tablet can be extrapolated to the lower strengths. A separate study for the lower strength formulations can be waived.

Based on the submitted bioequivalence study Buprenorphine/Naloxone G.L.(Pinewood) SL tablets (8/2 mg, 4/1 mg, 2/0.5 mg) are considered bioequivalent with Suboxone® SL tablets.

The results of the study with the 8/2 mg formulation can be extrapolated to other strengths (4/1 mg, 2/0.5 mg), according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Legal Status
The medicinal product is subject to special medical prescription.

User Testing
A separate User Testing is not required given that the reference product was approved via the centralised procedure. The Applicant Pinewood Laboratories Ltd. provided a Bridging Report for the PIL of Bupronox SL tablets (daughter PIL) to the reference Suboxone Sl Tablets PIL (parent PIL).

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant 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.

Summary Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The MAA 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 related to the medicinal product(s) applied for authorisation.

Safety specification
The MAH listed the following safety concerns:

Summary of safety concerns	
Important identified risks	• Abuse, misuse and diversion • Use in patients with hepatic impairment • Hepatic disorders • Drug withdrawal syndrome • Use during pregnancy and lactation leading to opioid toxicity or withdrawal in the child
Important potential risks	• None
Missing information	• None

The safety concerns are in line with the reference medicinal product. The proposed safety concerns are endorsed.

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

The specific adverse reaction follow-up questionnaires are aligned with reference medicinal product, and they are presented in Annex IV of RMP, 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 0.1, signed on 3 June 2024 is considered acceptable.

After approval 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.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

V. OVERALL CONCLUSIONS

BENEFIT RISK ASSESSMENT
Based on the submitted bioequivalence study Buprenorphine/Naloxone G.L. (Pinewood) SL tablets (8/2 mg, 4/1 mg, 2/0.5 mg) are considered bioequivalent with Suboxone® SL tablets.

The results of the study with the 8/2 mg formulation can be extrapolated to other strengths (4/1 mg, 2/0.5 mg), according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Overall, the benefit-risk-balance is considered to be positive.

Based on the review of the data on quality, safety and efficacy, the application for "*Nalopren 2 mg/0,5 mg Sublingualtabletten*", "*Nalopren 4 mg/1 mg Sublingualtabletten*" and "*Nalopren 8 mg/2 mg Sublingualtabletten*"is approved. For intermediate amendments see current product information.

VI. REVISION DATE

January 2025

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer from DE to IE	DE/H/7696/01-03/DC to IE/H/1386/001-003/DC	NA	13/01/2025	13/01/2025