COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bunalict 2 mg/0.5 mg and 8 mg/2 mg, tablets for sublingual use

(buprenorphine/naloxone)

NL/H/5829/001-002/DC

Date: 8 May 2023

This module reflects the scientific discussion for the approval of Bunalict 2 mg/0.5 mg and 8 mg/2 mg, tablets for sublingual use. The procedure was finalised at 21 September 2017 in Germany (DE/H/4890-93/001-002/DC). After a transfer on 1 May 2023, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Bunalict 2 mg/0.5 mg and 8 mg/2 mg, tablets for sublingual use, 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.

II. EXECUTIVE SUMMARY

II.1 Problem statement

This decentralised application concerns a generic version of buprenorphine HCl and naloxone HCl, under the trade names Bunalict 2 mg/0.5 mg and 8 mg/2 mg, tablets for sublingual use.
Ethypharm has developed 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 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, Ethypharm applied for the Marketing Authorisations for Bunalict 2 mg/0.5 mg and 8 mg/2 mg, tablets for sublingual use in BE, DK, ES, FI, HR, NL, NO, SE, SI (all DE/H/4890/001-002/DC), IT (DE/H/4891/001-002/DC), BG, HR, SI (DE/H/4892/001-002/DC) and the UK (DE/H/4893/001-002/DC).

II.2 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. 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.
The analgesic potency of BUP is 25- to 50-fold higher than morphine at low doses (<0.8 mg).
Effect of the opioid receptor antagonist naloxone is dependent of the route of administration. After sublingual administration of BNX, the absorption of naloxone is minimal and the opioid agonist effect of BUP predominates.

However, when the BNX tablets are crushed and injected, naloxone antagonizes the opioid agonist effect of BUP and would precipitate withdrawal.
The addition of naloxone to BUP may thus decrease the abuse liability of BUP to be injected.
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.

II.3 General comments on the submitted dossier

The MAA was be submitted according to Article 10(1)-Generic application of directive 2001/83/EC as amended and was supported by demonstrating bioequivalence between the generic and the reference product.

II.4 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.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
Regarding the statement on GMP for the active substances Buprenorphine hydrochloride and Naloxone hydrochloride dihydrate, statements/declarations are provided for all active substances manufacturing sites from the manufacturer Ethypharm responsible for manufacture of the finished product and batch release situated in the EU.
The clinical and bioanalytical site of BE study BPN01061/001 were inspected by European Authorities several times over recent years. No critical findings were made.

III. QUALITY ASPECTS

III.1 Drug Substance

The active substances Buprenorphine hydrochloride and Naloxone hydrochloride dihydrate are monographed in European Pharmacopoeia.
The active substances are supplied by three manufacturers each. All active substance manufacturers are holder of a valid CEP.
Active substance specification considering all additional tests listed in the respective CEP has been provided by the finished product manufacturer for both active substances.

Batch analytical data provided for both Buprenorphine hydrochloride and Naloxone hydrochloride dihydrate meet the specification limits.

III.2 Medicinal Product

The drug products are Bunalict 2 mg/0.5 mg and 8 mg/2 mg, tablets for sublingual use.
The composition of both strengths is dose-proportional.
The drug products are manufactured by Ethypharm in France.
In general, the information presented on the quality of the drug product is considered acceptable to guarantee the quality of the Buprenorphine/Naloxone sublingual tablets.
The excipients, manufacturing process and in-process controls of the drug product correspond to the current standard of pharmaceutical technology and are suitable to guarantee an appropriate product quality.
The description of the analytical test methods is adequate. The validation results are plausible in general.
Relevant quality criteria are specified in accordance with internationally acknowledged pharmacopoeias.
The tablets are packed in blister packaging.
A Certificate confirming the child resistance characteristic of the primary packaging according to EU standard EN 14375 has been provided.
Real-time stability data up to 18 months have been submitted for the long-term storage conditions and 6 months real-time data are available for the accelerated storage conditions.
Based on the updated real-time stability data and the outcome of a newly conducted photostability study, the shelf life of 2 years with the special storage conditions “Do not store above 30°C” and “Store in the original package in order to protect from light” is accepted.

IV. NON-CLINICAL ASPECTS

IV.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bunalict 2 mg/0.5 mg and 8 mg/2 mg, tablets for sublingual use are 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.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of buprenorphine and of naloxone as well as those of their combination are well known. As buprenorphine and naloxone are widely used, well-known active substances, the applicant has not provided additional non-clinical studies and further non-clinical studies are not required. Overview based on literature review is, thus, appropriate.
The submitted non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology of the combination of buprenorphine and naloxone is adequate.

V. CLINICAL ASPECTS

V.1 Pharmacokinetics

To support the application, the applicant has submitted one single dose bioequivalence study in fasting conditions, performed between Buprenophine/Naloxone sublingual tablets and Suboxone® sublingual tablets on the highest strength, 8/2 mg (buprenorphine/naloxone, respectively) (Study BPN01061/001). Based on the dose proportional composition of the two tablet strengths, the data obtained for the 8/2 mg tablet can be extrapolated to the lower strength, and thus a separate study for the 2/0.5 mg formulation can be waived.
Bioequivalence between the test and reference 8/2 mg sublingual tablets was demonstrated for the buprenorphine and unconjugated naloxone analyte after single dose administration.

V.2 Risk Management Plan

The MAH committed that the submitted RMP is in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to their active substance(s).
Additionally, the MAH should ensure that the RMP is fully in line with the current "Guideline on good pharmacovigilance practices (GVP) Module V – Risk Management systems (Rev. 1) and the "Guidance on format of the risk management plan (RMP) in the EU (EMA/465932/2013 , Rev.1 accompanying GVP Module V, Rev. 1) and that the published list of active substances and trademarks for which educational material as additional risk minimization measure is mandatory and provided: http://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Risikoinformationen/EducationMaterial/Tabelle-educatmaterial.html has been taken into account.
The MAH further committed that the summary of safety concerns and all corresponding sections of the RMP, including all risk minimization measures and pharmacovigilance measures are aligned with the RMP for the originator or similar products as adopted by CHMP (EPAR), published on: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125 and/or CMD(h), published on: www.hma/464.html.

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.

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.

VI. USER CONSULTATION

Overall, the test methodology follows the guidelines of the European Commission (Guideline on the readability of the label and package leaflet of medicinal products for human use, Revision January 2009; Update of Directive 2001/83/EC as amended by Directive 2004/27/EC / Guidance concerning consultations with target patient groups for the packet leaflet, May 2006). Both the first and the second test round met the success criteria of more than 90% of the subjects being able to locate the requested information, and of those, more than 90% being able to give the correct answer, to indicate that they understood the information presented. The general impression of the PL (Content, language and layout) was mostly positive. In conclusion, the user test is considered acceptable.

VII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Since bioequivalence between the test and reference SL tablets could be demonstrated, the benefit risk balance is positive from the clinical perspective. The application is approved. For intermediate amendments see current product information.

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
-	-	-	-	-	-