LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Buprefarm
(buprenorphine)

SE/H/1630/05-07/DC

This module reflects the scientific discussion for the approval of Buprefarm. The procedure was finalised on 2020-08-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Buprefarm, 25 µg/h, 30 µg/h and 40 µg/h, transdermal patch, submitted according to Article 10(3) of Directive 2001/83/EC, is a new strength / line extension of the previously authorised Buprefarm, 5 µg/h, transdermal patch, marketed by Orifarm Generics AB since 2016-06-16. The applicant, Orifarm Generics A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Temgesic, 0.2 mg, sublingual tablet authorised in DE since 1982, with Indivior UK limited as marketing authorisation holder.

This application refers to another hybrid application according to Article 10(3) of Directive 2001/83/EC: Norspan, 40 µg/h, transdermal patch from DE, with Mundipharma GmBH as marketing authorisation holder; itself in turn referring to Temgesic. Norspan was recommended for use in bioequivalence studies by the CMDh as an addition to the Scientific Advice held at the BfArM on 28th of June 2012.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

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

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

III.1 Introduction

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

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Buprefarm is a hybrid/generic product, it is not anticipated to lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

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

IV. CLINICAL ASPECTS

IV.1 Introduction

Buprenorphine is a partial agonist opioid, acting at the mu opioid receptor. It also has antagonistic activity at the kappa opioid receptor. Buprenorphine has been widely used for three decades and has proved to be a strong analgesic in relieving moderate to severe pain. The form of transdermal patches containing buprenorphine is also now available for more than one decade. The transdermal delivery system (TDS) provides rate-controlled release of buprenorphine over a period of seven days.

The proposed indication is:

Treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia.
Buprefarm is not suitable for the treatment of acute pain.
Buprefarm is indicated in adults.

The patch should be administered every 7th day.

IV.2 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted three bioequivalence studies comparing Buprefarm transdermal patch with the "reference" hybrid product Norspan.

Pharmacokinetic properties of the active substance
Absorption: Following buprenorphine application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for "buprenorphine 10 microgram/hour" to deliver detectable buprenorphine concentrations (25 picograms/ml) was approximately 17 hours. Analysis of residual buprenorphine in patches after 7-day use shows 15 % of the original load delivered. A study of bioavailability, relative to intravenous administration, confirms that this amount is systemically absorbed. Buprenorphine concentrations remain relatively constant during the 7-day patch application.

Elimination: After removal of buprenorphine, buprenorphine concentrations decline, decreasing approximately 50 % in 12 hours (range 10–24 h).

Study BPR-BESD-05-TFB/14
Methods
The study was an open, randomised, two-period, crossover, single dose study conducted in 32 healthy male and female volunteers. The subjects were dosed with 20 µg/h buprenorphine transdermal patch of either test or reference product.

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

Table 1. Pharmacokinetic Data for Buprenorphine in Study BPR-BESD-05-TFB/14

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)	
	Test product	Reference product
$AUC_{(0-t)}$ [pg/ml x h]	35711.104 ± 13561.134	34001.327 ± 11296.199
$AUC_{(0-inf}$ [pg/ml x h]	36275.131 ± 13632.763	34542.606 ± 11370.575
C_{max} [pg/ml]	299.462 ± 215.466	267.684 ± 154.300
T_{max} [h][1]	120.000 [12.500-216.000]	84.500 [12.500-169.000]

[1]Median (Min - Max)

Table 2. The 90 % confidence intervals of the primary bioequivalence parameters for Buprenorphine mean treatment T/R ratios were:

Test name	Parameter	Test value (T/R)	Lower 90% CL	Upper 90% CL
Classic 90% CI	C_{max}	106.34	97.33	116.19
Classic 90% CI	AUC_{0-t}	102.98	96.77	109.60
Classic 90% CI	AUC_{0-inf}	103.04	96.83	109.66

For AUC_{0-t}, AUC_{0-inf} 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 BPR-BEMD-07-TFB/14

Methods

The study was an open, randomised, two-period, crossover, multiple dose study conducted in 32 healthy male volunteers. The subjects were dosed with 20 µg/h buprenorphine transdermal patch of either test or reference product.

Results

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

Table 3. Pharmacokinetic Data for Buprenorphine in Study PBR-BEMD-07-TFB/14

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)	
	Test product	Reference product
$(AUC_{0\text{-}tau})_{ss}$ [pg/ml x h]	35978.087 ± 12256.242	36202.691 ± 11866.356
$C_{max,ss}$ [pg/ml]	309.965 ± 146.190	309.261 ± 115.145
$C_{min,ss}$ [pg/ml]	197.959 ± 67.970	177.792 ± 58.345
$T_{max,ss}$ [h][1]	72.030 [0.530-168.030]	59.530 [1.030-120.030]

[1]Median (Min - Max)

Table 4. The 90 % confidence intervals for buprenorphine mean treatment T/R were:

Test name	Parameter	Test value (T/R)	Lower 90% CL	Upper 90% CL
Classic 90% CI	$C_{max,ss}$	98.461	86.544	112.020
Classic 90% CI	$C_{min,ss}$	110.234	98.099	123.870
Classic 90% CI	$(AUC_{0\text{-}tau})_{ss}$	99.217	90.904	108.291

For $AUC_{0\text{-}tau,ss}$, $C_{min,ss}$ and $C_{max,ss}$ 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 BPR-BESD-13-TFB/17

Methods

This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Buprefarm, 40 µg/h, transdermal patch with Norspan, 40 µg/h, transdermal patch under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 288.0 hours post-dose. Plasma concentrations of buprenorphine were determined with an HPLC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max}. The study was conducted between 2018-07-25 and 2018-09-25.

Results

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

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for buprenorphine, n=29.

Treatment	AUC_{0-t} pg*h/ml	$AUC_{0-\infty}$ pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**70635 ± 23346**	**71830 ± 23770**	**572 ± 236**	**96 (42-168)**
Reference	**70250 ± 26892**	**71624 ± 27166**	**538 ± 224**	**78 (24-169)**
***Ratio (90% CI)**	**101.78 (96.28 – 107.60)**	**101.43 (95.87 – 107.31)**	**106.21 (96.35 – 117.08)**	**-**

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 %.

A biowaiver was sought for the additional strengths of 25 µg/h and 30 µg/h.

Discussion and overall conclusion

The studies BPR-BESD-05-TFB/14 and BPR-BEMD-07-TFB/14 submitted in support of the already approved strengths were assessed as part of the initial approval procedure.

For study BPR-BESD-13-TFB/17 the bioequivalence study and its 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.

Absence of studies with the additional strengths of 25 µg/h and 30 µg/h is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) are fulfilled.

Based on the submitted bioequivalence studies, Buprefarm is considered bioequivalent with Norspan.

IV.3 Pharmacodynamics

N/A

IV.4 Clinical efficacy

The placebo-controlled studies of transdermal Buprenorphine in the published literature were summarised and discussed by the applicant. The efficacy and safety of the transdermal patches with release rates varying between 5-20 µg/h and 10-40 µg/h were demonstrated in patients with low back pain or OA based on the published studies.

IV.5 Clinical safety

Skin tolerance was evaluated in both the bioequivalence studies as well as in the adhesion study (BPR-BESD-13-TFB/17). The statistical analysis of objective and subjective irritation scores showed that the test patch was equivalent to the respective reference patch with regards to skin tolerance.

IV.6 Risk Management Plans

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 Buperfarm.

Safety specification

Summary of safety concerns	
Important identified risks	• Respiratory depression • Accidental overdose • Drug withdrawal • Drug abuse and dependence
Important potential risks	• Medication error
Missing information	• Use in pregnant or breastfeeding patients • Paediatric use

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 12.09.2019 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.

IV.7 Discussion on the clinical aspects

Based on the submitted bioequivalence studies, Buprefarm is considered bioequivalent with

Norspan. Absence of studies with the additional strengths of 25 µg/h and 30 µg/h is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) are fulfilled.

The application contains an adequate review of published clinical data. Acceptable adhesion performance has been adequately shown. In addition, skin tolerance was evaluated in both the bioequivalence studies as well as in the adhesion study. The statistical analysis of objective and subjective irritation scores is equivalent to the respective reference patch with regards to skin tolerance.

Buprefarm is approvable from a clinical point of view.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Buprefarm 15 microgram/hour, SE/H/1630/X/06/G. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product has been found adequate. Bioequivalence has been shown.
The application contains an adequate review of published clinical data. Acceptable adhesion performance has been adequately shown. In addition, skin tolerance was evaluated in both the bioequivalence studies as well as in the adhesion study. The statistical analysis of objective and subjective irritation scores is equivalent to the respective reference patch with regards to skin tolerance. There are no objections to approval of Buprefarm from neither non-clinical nor clinical point of view. The product information is acceptable.

Overall, the benefit/risk ratio for the line extension is considered positive and Buprefarm, 25 µg/h, 30 µg/h and 40 µg/h, transdermal patch, is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Buprefarm, 25 µg/h, 30 µg/h and 40 µg/h, transdermal patch, was positively finalised on 2020-08-20.

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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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