Decentralised Procedure

Public Assessment Report

Bupre-HEXAL / Buprenorphin - 1 A Pharma 7 Tage 5 / 10 / 15 / 20 Mikrogramm/Stunde transdermales Pflaster

Buprenorphine

DE/H/4045-4046/001-004/DC

Applicants:
HEXAL AG, Germany;
1 A Pharma GmbH, Germany

Reference Member State	DE

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Bupre-HEXAL / Buprenorphin - 1 A Pharma 7 Tage 5 / 10 / 15 / 20 Mikrogramm/Stunde transdermales Pflaster
Name of the drug substance (INN name):	Buprenorphine
Pharmaco-therapeutic group (ATC Code):	N02AE01
Pharmaceutical form(s) and strength(s):	Transdermal patch 5 / 10 / 15 / 20 µg/h
Reference Number(s) for the DCP:	DE/H/4045-4046/001-004/DC
Reference Member State:	DE
Concerned Member States:	**DE/H/4045/001+004/DC:** AT, BE, CZ, DK, ES, FI, HR, IE, LU, NL, NO, PL, PT, SE, UK **DE/H/4045/002/DC:** AT, BE, CZ, DK, FI, HR, IE, LU, NL, NO, PL, PT, SE, UK **DE/H/4045/003/DC:** AT, BE, CZ, DK, FI, HR, IE, LU, NL, PL, PT, SE, UK **DE/H/4046/001-004/DC:** AT, IT
Applicant (name and address)	**DE/H/4045/001-004/DC:** HEXAL AG Industriestr. 25, D-83607 Holzkirchen, Germany **DE/H/4046/001-004/DC:** 1 A Pharma GmbH Keltenring 1+3, D-82041 Oberhaching, Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the applications for *Bupre-HEXAL 7 Tage 5 / 10 / 15 / 20 Mikrogramm/Stunde transdermales Pflaster* and *Buprenorphin – 1 A Pharma 5 / 10 / 15 / 20 Mikrogramm/Stunde transdermales Pflaster*, in the treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia, is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.2 About the product

Buprenorphine is a potent opioid analgesic, a semi-synthetic derivate of the opium alkaloid thebaine. It acts as a partial agonist at the μ-opiate receptor while exercising antagonist properties at κ- and δ-receptors. The analgesic potency of buprenorphine is 25-50 times higher (on a weight by weight basis) than that of morphine. Buprenorphine has been widely used for two decades and has proved to be a strong analgesic in relieving moderate to severe acute (e.g. post-operative) and chronic pain of malignant and non-malignant origin.

The product being subject of this procedure is a transdermal delivery system (TDS). By contrast to the marked fluctuations in plasma concentrations observable after using conventional routes of administration (sublingual tablets or injections) of buprenorphine, the rate-controlled release of buprenorphine from the transdermal patch should ensure relatively constant serum levels which translate into long-term and consistent pain relief with the chance of minimising the occurrence of side effects.

The proposed indication is:
Treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia
Not suitable for the treatment of acute pain.

The patch should be administered every seven days.

The proposed indication is in line with the already approved indication of Norspan®.

II.3 General comments on the submitted dossier

The application for marketing authorisation for Buprenorphine 5 µg/h, 10 µg/h, 15µg/h and 20 µg/h transdermal patches is made under article 10(3), hybrid application of Directive 2001/83/EC as amended. Reference is made to the preclinical and clinical data of TEMGESIC® sublingual tablets, RB Pharmaceutical Limited. This originator product was approved in Germany on 22nd December 1982.

Compared to TEMGESIC® sublingual tablets the product being subject of this procedure is

- different with regard to the pharmaceutical form (tablet vs. TTDS),
- different with regard to the strength (0.2/0.4mg vs. 5/10/15/20 Mikrogramm/h), and
- different with regard to the route of administration (s.l. vs. transdermal).

The applicant refers also to the clinical data provided for Norspan®. Norspan® is also a seven-day patch and was first approved in Denmark on 16 July 2003. The product was also approved in different European MS via mutual recognition procedure (DK/H/0718). The marketing authorisation for Norspan® was granted based on article 10(3) of Directive 2001/83/EC.

With Germany acting as RMS, Hexal AG and 1A Pharma GmbH are applying for the Marketing Authorisations of "Bupre-HEXAL 7 Tage 5 / 10/ 15 / 20 Mikrogramm/Stunde transdermales Pflaster" and „Buprenorphin – 1 A Pharma 7 Tage 5 / 10 / 15 / 20 Mikrogramm/Stunde transdermales Pflaster" in AT, BE, CZ, DK, ES, FI, HR, IE, LU, NL, NO, PL, PT, SE, UK (DE/H/4045/001+004/DC), AT, BE, CZ, DK, FI, HR, IE, LU, NL, NO, PL, PT, SE. UK (DE/H/4045/002/DC), AT, BE, CZ, DK, FI,

HR, IE, LU, NL, PL, PT, SE, UK (DE/H/4045/003/DC) and AT, IT (DE/H/4046/001-004/DC), respectively, as CMS.

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.

The applicant confirms that the (pivotal) bioequivalence study was conducted in accordance with GCP, GLP and relevant regulatory guidance from competent authorities.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Certificates of Suitability (CoS) have been provided for the suppliers of the drug substance buprenorphine.
The quality of the drug substance is controlled according to pharmacopoeial requirements.
Analytical methods used to analyse the active substance are validated.
A re-test period of 3 years and 4 years, respectively, is stated in the CEPs.

Drug Product

The development of the finished product as transdermal patches has been described, the choice of excipients is justified and their functions explained. Relevant quality characteristics of the drug substance and the drug product are specified. The proposed limits are in general accepted.
The ingredients and the manufacturing process of the drug product are considered suitable to produce a pharmaceutical product of the appropriate quality.
The description of the test methods used to analyse the drug substance and drug product are adequate, the validation results are plausible.
Batch analysis shows that the finished product meets the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are in general adequately drawn up. On the basis of the submitted stability data, a shelf-life of 18 months with the precaution "Do not store above 25°C" has been accepted for all 4 strengths 5, 10, 15 and 20 mg.

III.2 Non-clinical aspects

Pharmacology, Pharmacokinetics, Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of buprenorphine are well known. As buprenorphine is a widely used, well-known active substance, 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 non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology of buprenorphine is adequate.

Environmental Risk Assessment (ERA)

Since the medicinal products 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.

III.3 Clinical aspects

Pharmacokinetics

The applicant has submitted as report the following clinical trials:

- A Pilot study (Study code: 2010-35-TTS-1, EudraCT-No. 2010-022542-24)
- A Pivotal single / multiple dose study (Study code: 2011-47-TTSM-2)
- A skin adhesion study (Study code: 2013-15-TTS-3)

Pharmacokinetic Parameters

The pivotal single / multiple dose BE study was adequately designed and conducted. The study demonstrates bioequivalence between the test and the reference patch (Norspan®) with respect to the rate and extent of buprenorphine exposure after single and multiple dose application for the highest strengths (20µg/h).

Waiver for additional strengths

In order to justify a waiver for additional strengths, the applicant takes reference to the New Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1):

- The qualitative composition is the same for all strengths;
- The strengths are proportional to the effective surface area of the patch and the lower dose strengths can be considered as "partial" areas of the highest dose strength;
- There are similar dissolution/release profiles.

Thus, waiving *in vivo* bioequivalence testing for the additional strengths being subject of this application (5, 10 and 15µg/h) is acceptable.

Adhesion Performance Evaluation

Comparability of the adhesion properties of the buprenorphine 20 µg/h patch have been tested in the submitted bioequivalence study No. 2011-47-TTSM-2. The adhesion results showed non-inferiority of the test patch to the reference product (the lower limit of the confidence interval for the difference of adhesiveness was above -10%). Thus, the appropriateness of the adhesion performance of the test product has been proven.

Also, the adhesion properties of the smallest patch (5 µg/h patch) have been tested in the skin adhesion study No. 2013-15-TTS-3 showing similar adhesion characteristics of the smallest test patch (5µg/h) and the largest test patch (20µg/h).

Pharmacodynamics

N/A

Clinical efficacy

N/A

Clinical safety

After request of the RMS and several CMSs the applicant presents now a product with an integrated cover patch in order to ensure patient's safety/compliance.

Skin Tolerance Evaluation

The product's potential of local irritation was evaluated within the submitted bioequivalence study No. 2011-47-TTSM-2 and it has been shown that there were no differences for the safety profiles between the two treatments compared. Additional skin sensitization and irritation studies are not necessary since the quantitative and qualitative composition of test and reference product are very similar.

Legal Status

Subject to medical prescription

User Testing
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). This readability test result illustrates a positive assessment of the Buprenorphine package insert. The general impression of the PL (Content, language and layout) was mostly positive. In conclusion, the user test is accepted.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/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

Important identified risks	• Respiratory depression • Abuse, misuse and diversion • Drug dependence and withdrawal • Accumulation of buprenorphine in patients with hepatic impairment
Important potential risks	• Accidental exposure • Medication errors • Overdose • Off-label use in the treatment of chronic pain in paediatric patients
Missing information	• Safety and efficacy of use during pregnancy and lactation • Safety and efficacy in paediatric patients

No additional pharmacovigilance or risk minimization activities were proposed.

Periodic Safety Update Report (PSUR)
Buprenorphin is listed in the list of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised. PSURs shall be submitted in accordance with the requirements set out in this list. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV. BENEFIT RISK ASSESSMENT
The bioequivalence study 2011-47-TTSM-2 has demonstrated bioequivalence between the test and the reference patch (Norspan®) with respect to the rate and extent of buprenorphine exposure after single and multiple dose application for the highest strengths (20µg/h). Comparability of the adhesion properties of the buprenorphine 20 µg/h patch has been also tested in study 2011-47-TTSM-2. In addition, comparability of the adhesion properties of the buprenorphine 5 µg/h test patch with the 20µg/h test patch has been tested in the skin adhesion study 2013-15-TTS-3. Overall, appropriateness of the adhesion performance of the product being subject of this procedure has been adequately proven. The product's potential of local irritation was evaluated within the study No. 2011-47-TTSM-2 and it has been shown that there were no differences for the safety profiles between the two treatments compared. Overall, the benefit-risk-balance for the products as applied for is positive.
The application is approved.
For intermediate amendments see current product information.