Decentralised Procedure

Public Assessment Report

Buprenoratiopharm 35 Mikrogramm/Stunde; 52,5 Mikrogramm/Stunde; 70 Mikrogramm/Stunde Transdermales Pflaster (a.o.)

Buprenorphine

DE/H/5078-5079/001-003/DC

Applicant: ratiopharm GmbH

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	DE/H/5078: Buprenoratiopharm DE/H/5079: Buprenorphin AbZ 35 Mikrogramm/Stunde; 52,5 Mikrogramm/Stunde; 70 Mikrogramm/Stunde Transdermales Pflaster
Name of the drug substance (INN name):	Buprenorphine
Pharmaco-therapeutic group (ATC Code):	N02AE01
Pharmaceutical form(s) and strength(s):	35 µg/h / 52.5 µg/h / 70 µg/h transdermal patch
Reference Number(s) for the Decentralised Procedure	DE/H/5078-5079/001-003/DC
Reference Member State:	DE
Concerned Member States:	DE/H/5078: AT, BE, ES, FI, HR, IS, NL, PL, PT, UK DE/H/5079: ES
Applicant (name and address)	ratiopharm GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for buprenorphine 35 µg/h, 52.5 µg/h, 70 µg/h transdermal patches, in the treatment of "moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics", is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

For generic application this section is not applicable.

II.2 About the product

Buprenorphine is a centrally-acting-analgesic that binds to the opioid receptors with high affinity. It acts as a partial µ-opioid receptor agonist as well as a κ-opioid receptor antagonist that may contribute to the high analgesic potential that is associated with relatively low dependence potential. Buprenorphine slowly dissociates from µ-opioid receptors, which results in a slow onset but relatively long duration of analgesic action.

In pain models, buprenorphine showed a broad analgesic and antihyperalgesic profile and was more and longer effective than e.g. morphine or fentanyl. In contrast to other opiate analgesics, buprenorphine showed an antihyperalgesic effect and a ceiling effect on respiratory function at higher dosages.

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.

Buprenorphine as a transdermal delivery system (TDS) was approved in Germany in 2001 (Transtec and Tridol, Gruenenthal GmbH). Buprenorphine TDS is indicated for the treatment of moderate to severe pain which does not respond to non-opioid analgesics. 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. Three dose strengths of the Buprenorphin transdermal patch have been developed, which should enable constant and linear delivery rates of the active substance from the transdermal system.

II.3 General comments on the submitted dossier

This decentralised application concerns a generic version of buprenorphine 35 µg/h, 52.5 µg/h, 70 µg/h transdermal patches. The application for marketing authorisation is made under article 10(1), generic application of Directive 2001/83/EC as amended.

The application refers to the original medicinal product Transtec PRO® 35 µg/h, 52.5 µg/h, 70 µg/h transdermal patches manufactured and marketed by Grünenthal GmbH. The first marketing authorisation for the original product within the EU was granted for Transtec PRO® transdermal patches in Germany on July 24, 2001 to Grünenthal GmbH.

With Germany as the Reference Member State in this Decentralised Procedure, the applicant ratiopharm GmbHis applying for the Marketing Authorisations for "Buprenorphin 35 / 52,5 / 70 µg/h transdermal patch" in DE/H/5078: AT, BE, ES, FI, HR, IS, NL, PL, PT, UK and DE/H/5079: ES as CMS.

A scientific advice has been sought from the BfArM on the clinical program on 28th of June 2012.

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.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
The Clinical Centre of 3S, Cumparatura, Suceava County, DN2, 727046 Romania has been inspected on 14 – 17 July 2015. The GCP inspection was considered necessary in order to verify the quality and validity of the submitted data and to check whether the BE-trial BPR-BEMD-03-TFB/12 (Eudra-CT-No. 2012-005033-3) was performed in conformity with ICH GCP. According to the *Final* inspection report (dated 27th August 2015) "the inspected trial can be considered as having been conducted in compliance with GCP and the data generated are considered as reliable".

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The active substance used for the manufacture of the transdermal patches is supplied by three manufacturers. Two of the manufacturers are holders of a valid CEP whereas the third manufacturer has applied an ASMF procedure.

The chemical-pharmaceutical documentation in relation to the active substance buprenorphine is of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product have been adequately drawn up.

A re-test period of 4 years for buprenorphine sourced from the first manufacturer, a re-test period of 3 years for buprenorphine supplied by the second manufacturer has been approved, if stored in the container as mentioned in the corresponding CEP.
Stability studies have been performed with buprenorphine supplied by the third manufacturer. No significant changes in any parameters were observed. The proposed retest period of 18 months is considered justified.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 12 batches. The batch analysis results show that the finished products meet 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 have been adequately drawn up.

Due to updated stability data from the finished product manufacturer and considering the possibility of extrapolation stated in Annex II of the guideline the Guideline *CPMP/QWP/122/02,rev 1 corr*, the proposed shelf-life of 24 months without any storage caution can be accepted.

III.2 Non-clinical aspects

Pharmacology, pharmacokinetics and toxicology

The general non-clinical 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 in this regard and the applicant provides none. Overview based on literature review is, thus, appropriate in this respect.

The submitted non-clinical overview on the general non-clinical pharmacology, pharmacokinetics and toxicology of buprenorphine is considered adequate.

Local tolerance of the generic buprenorphine patches has not been evaluated in non-clinical studies. However, this is considered acceptable, since skin tolerance was evaluated in both submitted bioequivalence studies as well as in the submitted clinical adhesion study and since the statistical analysis of objective and subjective irritation scores observed during the studies indicated that the test patches are equivalent to the respective reference patch in regards to skin tolerance (see Clinical Assessment).

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

To support the application, the applicant has submitted as study report the following clinical trials:

- Single Dose Bioequivalence Study (Study no. BPR-BESD-02-TFB/12): "*OPEN LABEL, TWO-PERIOD, TWO-SEQUENCE, TWO-WAY CROSSOVER, CONTROLLED, RANDOMIZED, SINGLE DOSE STUDY TO ASSESS BIOEQUIVALENCE, SKIN TOLERANCE AND ADHESION PERFORMANCE OF Buprenorphin TDS 70 µg/h transdermal patch (TEST FORMULATION) VERSUS Transtec PRO® 70 Mikrogramm/h transdermales Pflaster (REFERENCE FORMULATION) APPLIED TOPICALLY TO HEALTHY MALE AND FEMALE VOLUNTEERS UNDER FASTING CONDITIONS*."
- Multiple Dose Bioequivalence Study (Study no. BPR-BEMD-03-TFB/12): "*OPEN LABEL, TWO-PERIOD, TWO-SEQUENCE, TWO-WAY CROSSOVER, CONTROLLED, RANDOMIZED, MULTIPLE DOSE STUDY TO ASSESS BIOEQUIVALENCE, SKIN TOLERANCE AND ADHESION PERFORMANCE OF Buprenorphin TDS 70 µg/h transdermal patch (TEST FORMULATION) VERSUS Transtec PRO® 70 Mikrogramm/h transdermales Pflaster (REFERENCE FORMULATION) APPLIED TOPICALLY TO HEALTHY MALE VOLUNTEERS*."
- Patch Adhesion Assessment Study (Study no. BPR-AP-04-TFB/12): "*OPEN LABEL, TWO-PERIOD, TWO-SEQUENCE, TWO-WAY CROSSOVER, CONTROLLED, RANDOMIZED, SINGLE DOSE STUDY TO ASSESS ADHESION PERFORMANCE OF Buprenorphin TDS 35 µg/h transdermal patch (TEST FORMULATION) VERSUS Transtec PRO® 35 Mikrogramm/h transdermales Pflaster (REFERENCE FORMULATION) APPLIED TOPICALLY TO HEALTHY MALE AND FEMALE VOLUNTEERS*"

Pharmacokinetic Parameters

Studies BPR-BESD-02-TFB/12 and BPR-BEMD-03-TFB/12 have demonstrated bioequivalence between the test and the reference patch with respect to the rate and extent of buprenorphine exposure after single and after multiple dose application for the highest strengths (70µg/h).

Waiver for additional strengths

In order to justify biowaiving in-vivo bioequivalence data for the 35 and 52.5 µg/h strengths, the applicant takes reference to the actual Note for Guidance on modified release oral and transdermal dosage forms, section II (pharmacokinetic and clinical evaluation) (CPMP/EWP/280/96, 28 July 1999) for a Transdermal Delivery System (TDS) essentially similar to a marketed formulation:

- The Applicant provides evidence for the claim of linearity of buprenorphine in the respective dose range (see section 2.5.3; transtec-2009).
- All three dose strengths (35, 52.5 and 75 µg/h strengths) are fully dose proportional (the composition is the same, the strength is proportional to the effective surface area of the patch, and the lower dose strengths can be considered "partial" areas of the highest strength).
- Similar in vitro dissolution profiles were demonstrated between the test and reference product across the entire range of dose strengths.

Adhesion Performance Evaluation

Comparability of the adhesion properties of the buprenorphine 70 µg/h patch has been tested in study BPR-BESD-02-TFB/12 and BPR-BEMD-03-TFB/12. Also, comparability of the adhesion properties of the buprenorphine 35 µg/h patch has been tested in study BPR-AP-04-TFB/12. Appropriateness of the adhesion performance of the product being subject of this procedure has been adequately proven.

Pharmacodynamics

N/A

Clinical efficacy

N/A

Clinical safety

Skin Tolerance Evaluation

Skin tolerance was evaluated in both bioequivalence studies as well as in the adhesion study. The statistical analysis of objective and subjective irritation scores attributed during the studies that the test patch is equivalent to the respective reference patch in regards to skin tolerance.

Legal Status

POM

User Testing

Parent Leaflet:

- Buprenorphin-Actavis 35 / 52.5 / 70 micrograms/h transdermal patch as provided with the Public Assessment Report DE/H/3646/001-003/DC on the MRI product index

Daughter Leaflet:

- [Buprenorphin] 35 / 52.5 / 70 micrograms/h transdermal patch

The daughter leaflet is a generic medicinal product containing the active substance buprenorphine. Reference product is the originator product of Transtec transdermal patch, marketed by Grünenthal GmbH, Germany. Transtec has been authorised via Mutual Recognision Procedure DE/H/0307/001. The package leaflet has last been updated in July 2011 and is harmonised within the following EU countries: AT, BE, DK, DE, IE, IT, LU, PT, SL, ES, UK. The content of the package leaflet for the generic product has been taken from the reference product as far as possible. As parent leaflet the user tested package leaflet (PL) Buprenorphin-Actavis has been chosen. The text of the parent leaflet is as well highly similar to the text content of Transtec transdermal patch.

Bridging evaluation of content:

Since writing style of the parent leaflet has already been proven user/patient friendly and patients are able to act upon the information given, the text well serves as parent for the proposed daughter leaflet. Differences in content between parent leaflet and daughter leaflet: The content of the

daughter leaflet is widely identical to the one of the parent leaflet. A detailed comparison has been provided.
Identified differences derive mainly from product specific properties and/or adherence of the daughter text to the one of the originator. Further minor differences are due to obedience to QRD recommendations. All differences are well justified and do not affect the patient friendliness of the package leaflet.

Summary Pharmacovigilance system
The Applicant has submitted signed Summaries of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master Files fully comply with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summaries acceptable.

Risk Management Plan (RMP)
The applicant has submitted an updated RMP, including the following safety concerns.

Important identified risks	• Respiratory depression • Drug dependence and withdrawal • Abuse, misuse and diversion • Accidental exposure
Important potential risks	• n/a
Missing information	• Safety and efficacy of use during pregnancy and lactation • Safety and efficacy of use in paediatric patients < 18 years

No additional risk minimisation or pharmacovigilance activities have been suggested.

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)
- 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.
- In case the substance is not listed in the EURD list MAHs are strongly advised to submit their PSURs in accordance with the List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised which should be legally interpreted as a "coordinated" national request addressed to MAHs in accordance with Article 107c (2) of Directive 2001/83/EC as amended.
- 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

Studies BPR-BESD-02-TFB/12 and BPR-BEMD-03-TFB/12 have demonstrated bioequivalence between the test and the reference patch with respect to the rate and extent of buprenorphine exposure after single and after multiple dose application for the highest strengths (70µg/h). Comparability of the adhesion properties of the buprenorphine 70 µg/h patch has been tested in study BPR-BESD-02-TFB/12 and BPR-BEMD-03-TFB/12. Also, comparability of the adhesion properties of the buprenorphine 35 µg/h patch has been tested in study BPR-AP-04-TFB/12. Appropriateness of the adhesion performance of the product being subject of this procedure has been adequately proven. In addition, skin tolerance was evaluated in both bioequivalence studies as well as in the adhesion study. The statistical analysis of objective and subjective irritation scores attributed during the studies that the test patch is equivalent to the respective reference patch in regards to skin tolerance. Overall, the benefit-risk-balance for the products as applied for is positive.

The application is approved.

For intermediate amendments see current product information.