LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Buprefarm
(buprenorphine)

SE/H/1630/X/06/G

This module reflects the scientific discussion for the approval of Buprefarm. The procedure was finalised on 2018-10-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Orifarm Generics A/S has applied for a marketing authorisation for Buprefarm, 15 µg/h, transdermal patch. The active substance buprenorphine is the same as in Temgesic, 0.2 mg sublingual, marketed by RB Pharmaceuticals Limited since 1982-12-22.
No PAR is available for Buprefarm 5, 10, 20 µg/h.

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

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of buprenorphine has been provided, which was based on scientific literature.
Buprenorphine is a widely used, well-known active substance and since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

III.2 Ecotoxicity/environmental risk assessment

Approval of Buprefarm is not expected to result in an increased exposure of the active substance to the environment since the product is intended as a substitute for other identical products on the market.

III.3 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 Pharmacokinetics

To support the initial application of the previously authorised Buprefarm strengths (5 µg/h, 10 µg/h and 20 µg/h) the applicant submitted two pivotal bioequivalence studies (one single dose study and one multiple dose study) and one adhesion performance study in order to compare Buprefarm with the reference product Norspan. Bioequivalence was demonstrated with the highest formulation, 20 µg/h. Absence of studies with the additional strengths (5 µg/h and 10 µg/h) was acceptable. No bioequivalence studies have been conducted with the new 15 µg/h strength.

The different strengths 5 µg/h, 10 µg/h, 15 µg/h and 20 µg/h of Buprenorphine transdermal patches do all derive from the same drug laminate, so the qualitative composition is identical as well as the packaging material. The only difference between the four strengths is the patch size. The different drug release *in vivo* and *in vitro* is only based on size of the drug containing patch. New dissolution data for the 15 µg/h strength has been included, and the dissolution is similar to the other strengths, and thus justifies biowaiver of strength.

For this applied new strength, no bioequivalence studies are required according to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). Bioequivalence has previously been demonstrated with the highest formulation, 20 µg/h. All four dose strengths (5, 10, 15 and 20 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). The drug release *in vivo* and *in vitro* is only based on patch size. Similar dissolution has been demonstrated as discussed above. Thus, absence of studies with the new 15 µg/h strength is acceptable.

IV.2 Pharmacodynamics, clinical efficacy and clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety were submitted. This is acceptable, since the application concerned the addition of a new concentration, 15 µg/h, of the previously authorised product Buprefarm transdermal patch (5, 10 and 20 µg/h).

IV.3 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 Buprefarm, buprenorphine 5/10/15/20 µg/h transdermal patch.

Safety specification

Summary of safety concerns	
Important identified risks	• Respiratory depression • Drug dependence and withdrawal • Abuse, misuse, and diversion • Accidental exposure
Important potential risks	NA
Missing information	• Use during pregnancy and lactation • Use in paediatric patients < 18 years

Pharmacovigilance Plan

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
NA	Routine PhV: (1) Identification of any report of the addressed safety concerns in clinical practice (2) Collection of safety data from the published case reports, clinical studies, reviews or other publications Additional PhV: Not applicable	Routine surveillance of safety data

Important potential risks
None

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Respiratory depression	Contraindication in section 4.3 of the SPC: Buprenorphine is contraindicated in conditions in which the respiratory centre and function are severely impaired or may become so. Warning in section 4.4 of the SPC: Buprenorphine occasionally causes respiratory depression. Therefore care should be taken when treating patients with impaired respiratory function or patients receiving medicinal products which can cause respiratory depression. Warning in section 4.5 of the SPC: When buprenorphine is applied together with other opioids, anaesthetics, hypnotics, sedatives, antidepressants, neuroleptics, and in	None proposed

	general, medicinal products that depress respiration and the central nervous system, the CNS effects may be intensified. This applies also to alcohol. Listing in section 4.8 of the SPC: Dyspnoea, respiratory depression.	
Drug dependence and withdrawal	Warning in section 4.4 of the SPC: Buprenorphine has a substantially lower dependence liability than pure opioid agonists. In healthy volunteer and patient studies with buprenorphine, withdrawal reactions have not been observed. However, after long-term use of buprenorphine withdrawal symptoms, similar to those occurring during opiate withdrawal, cannot be entirely excluded. These symptoms are: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal disorders. Listed in section 4.8: Buprenorphine has a low risk of dependence. After discontinuation of buprenorphine, withdrawal symptoms are unlikely. This is due to the very slow dissociation of buprenorphine from the opiate receptors and to the gradual decrease of buprenorphine serum concentrations (usually over a period of 30 hours after removal of the last transdermal patch). However, after long-term use of buprenorphine withdrawal symptoms, similar to those occurring during opiate withdrawal, cannot be entirely	None proposed

	excluded. These symptoms include: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal disorders.	
Abuse, misuse, and diversion	Warning in section 4.4 of the SPC: Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics. In humans limited euphorigenic effects have been observed with buprenorphine. This may result in some abuse of the product and caution should be exercised when prescribing to patients known to have, or suspected of having, a history of drug abuse.	None proposed
Accidental exposure	Accidental exposure due to simultaneous application of several patches or too fast increase of the dose may result in overdose with symptoms such as respiratory depression, sedation, drowsiness, nausea, vomiting, cardiovascular collapse and marked miosis.	None proposed
Use during pregnancy and lactation	Information in section 4.6 of the SPC: There are no adequate data from the use of buprenorphine in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Towards the end of pregnancy high doses of buprenorphine may induce respiratory depression in the new-born infant even after a short period of administration.	None proposed

	Chronic administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the new-born infant. Therefore administration of buprenorphine is contraindicated during pregnancy. Buprenorphine is excreted in human milk. Studies in rats have shown that buprenorphine can inhibit lactation. Buprenorphine should not be used during breast-feeding.	
Use in paediatric patients < 18 years	Information in section 4.2 of the SPC: As buprenorphine has not been studied in patients under 18 years of age, the use of the medicinal product in patients below this age is not recommended.	None proposed

Summary of the RMP

The submitted Risk Management Plan, version 1.3 signed 2018-04-09 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.

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 the content of BuTrans (Norspan), DK/H/0718/001-003/. Regarding the layout bridging was made to Rivastigmin-neuraxpharm, DE/H/3403/001-002, and Kaliumklorid Orifarm, DK/H/2347/001.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Buprenorphine 15 µg/h transdermal patch, in the treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia, is considered approvable.

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

Post approval commitments

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, 15 µg/h, transdermal patch was positively finalised on 2018-11-14.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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