IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Espranor 8 mg Oral Lyophilisate
Buprenorphine
PA0549/024/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Espranor 2 mg Oral Lyophilisate and Espranor 8 mg Oral Lyophilisate, from Ethypharm, on <date of authorisation> for substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.
Treatment with Espranor oral lyophilisate is intended for use in adults and adolescents aged 15 years or over who have agreed to be treated for addiction.

The applications were submitted under a mutual recognition repeat use procedure with Ireland as the reference member state and Norway as the concerned member state.

The original decentralised procedure was submitted in 2014 under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be hybrid medicinal products of Subutex 2 mg and 8 mg sublingual tablets, with the UK as reference member state and Ireland as concerned member state in the following procedure UK/H/5385/001-002/DC. The products have been authorised in Ireland 14th July 2017.

A copy of the original PAR can be accessed in the link below.

https://mhraproducts4853.blob.core.windows.net/docs/60d0515c909e1f25041f7e6282e25525fcecf150

The RMS was transferred from the UK to Ireland on 11th February 2019. The current procedure number is IE/H/0972/001-002/DC.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Espranor 8 mg Oral Lyophilisate
Name(s) of the active substance(s) (INN)	Buprenorphine
Pharmacotherapeutic classification (ATC code)	N07BC01
Pharmaceutical form and strength(s)	8 mg Oral Lyophilisate
Marketing Authorisation Number(s) in Ireland (PA)	PA0549/024/002
Marketing Authorisation Holder	Ethypharm
MRP/DCP No.	IE/H/0972/002/E/01
Reference Member State	IE
Concerned Member State	NO

II. QUALITY ASPECTS

II.1. Introduction

This application is for Espranor 2 mg & 8 mg Oral Lyophilisate.

II.2 Drug substance

The active substance is Buprenorphine Hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

All aspects of the manufacture and control of the active substance, buprenorphine hydrochloride, are covered by a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The finished products are oral lyophilisates and contain 2 mg or 8 mg buprenorphine (as hydrochloride), as the active ingredient.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All excipients comply with their respective European Pharmacopoeia monographs with the exception of mint flavour which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Tablets / Oral lyophilisates and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. and EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Espranor 2 mg Oral Lyophilisate and Espranor 8 mg Oral Lyophilisate.

III. NON-CLINICAL ASPECTS

III.1 Introduction

These applications have been submitted in accordance with Article 10.3 (hybrid) of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of buprenorphine hydrochloride are well known. As buprenorphine hydrochloride is a widely used, well-known active substance, no new non-clinical data have been supplied and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology

No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics

No new data have been submitted and none are required for applications of this type.

III.4 Toxicology

No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment

Since the proposed 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.6 Discussion on the non-clinical aspects

There are no objections to the approval of Espranor 2 mg Oral Lyophilisate and Espranor 8 mg Oral Lyophilisate. from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

These applications were submitted in accordance with Article 10.3 (hybrid) of
Directive 2001/83/EC, as amended, with reference to Subutex 2 mg and 8 mg sublingual Tablets as marketed by RB Pharmaceuticals Ltd. Espranor 2 mg and 8 mg oral lyophilisate contain the same qualitative and quantitative composition in active substance, buprenorphine hydrochloride, as the reference products.

Espranor oral lyophilisate is designed to rapidly disperse (within 15 seconds) on the tongue compared to Subutex sublingual tablets which is placed under the tongue and takes 5 to 10 minutes to dissolve. Due to the higher bioavailability of Espranor (25-30%), bioequivalence could not be demonstrated through bioavailability studies as the buprenorphine is more completely absorbed from the Espranor 2 mg and 8 mg oral lyophilisate formulation compared with the lower amount absorbed from the Subutex formulation.

In order to bring the posology in line with Subuxone SmPC (most recently approved and with similar safety profile of Subutex), in terms of expected plasma concentration of buprenorphine, the starting and maximum doses of Espranor have been reduced to
2 mg and 18 mg respectively. This means that a similar response may be achieved with an overall lower exposure to buprenorphine. However, due to the known inter- individual variability of buprenorphine pharmacokinetics, the dosage should be titrated according to the patient's clinical response.

Consequently Espranor 2 mg and 8 mg oral lyophilisate and Subutex, although intended to treat the same indications, are not intended to be interchangeable products due to the slightly different posology.

IV.2 Pharmacokinetics

In support of these applications, the Marketing Authorisation Holder submitted

three bioequivalence studies: two pilot studies performed at the 2 mg and 8 mg dose strengths, and one pivotal study performed at the 8 mg dose strength. The Applicant demonstrated that the plasma concentrations achieved in their bioequivalence studies are within known safe limits for buprenorphine and that Espranor plasma levels achieved during the titration posology fall within the range of all sublingual buprenorphine products available in Europe, including Subutex and Subuxone.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Drugs used in opioid dependence, ATC code: N07BC01

The Espranor oral lyophilisate dosage form is designed to rapidly disperse on the tongue usually in less than 15 seconds.

Buprenorphine is an opioid partial agonist/antagonist which attaches itself to the μ (mu) and κ (kappa) receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible link with the μ receptors which, over a prolonged period, minimises the need of the addicted patient for drugs.

During clinical pharmacological studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, "good effect", and respiratory depression.

IV.4 Clinical Efficacy
In the two Phase II safety studies Espranor was shown to be as efficacious as Subutex in reducing cravings, holding subjects, and preventing withdrawal symptoms, and at the same dose. There were no statistically significant differences between Espranor and Subutex when the mean within subject changes in either OOWS or SOWS scores from Titration Day 7 to either Maintenance Days 2 or 7 were compared.

The Espranor oral lyophilisate quickly disintegrated when placed on the tongue;
96.3% of Espranor administrations achieved partial disintegration on the tongue in ≤
15 seconds and the median time for complete disintegration was 2.0 minutes.

IV.5 Clinical Safety

The Marketing Authorisation Holder (MAH) has submitted a risk management plan
(RMP), 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 Espranor 2 mg and 8 mg oral lyophilisate.

IV.6 Discussion on the clinical aspects

The grant of Marketing Authorisations is recommended.

V. OVERALL CONCLUSIONS

The quality of the products is acceptable, and no new non-clinical or clinical concerns
have been identified. The data supplied supports the claim that these products are hybrid medicinal products of the originator products, Subutex 2 mg and 8 mg sublingual tablets. Extensive clinical experience with buprenorphine hydrochloride is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.

VI. REVISION DATE

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