

Public Assessment Report

Decentralised Procedure

Espranor 2 mg and 8 mg oral lyophilisate

(buprenorphine hydrochloride)

Procedure No: UK/H/5385/001-02/DC

UK Licence No: PL 00156/0364-0365

Martindale Pharmaceuticals Ltd

LAY SUMMARY
Espranor 2 mg and 8 mg oral lyophilisate
(buprenorphine hydrochloride)

This is a summary of the public assessment report (PAR) for Espranor 2 mg and 8 mg oral lyophilisates (PL 00156/0364-0365; UK/H/5385/001-02/DC). It explains how Espranor 2 mg and 8 mg oral lyophilisates were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about Espranor 2 mg and 8 mg oral lyophilisates, patients should read the package leaflet or contact their doctor, pharmacist or nurse.

What are Espranor 2 mg and 8 mg oral lyophilisate and what are they used for?

The applications for Espranor 2 mg and 8 mg oral lyophilisates were submitted as hybrid medicines. They are similar to reference medicines containing the same active substance, but are available ‘as an oral lyophilisate’.

The reference medicines already authorised in the UK are Subutex 2 mg and 8 mg sublingual tablets (RB Pharmaceuticals Limited; PL 36699/0002-0003).

The company has provided additional safety data as well as a supportive safety study to demonstrate the safety and efficacy of Espranor 2 mg and 8 mg oral lyophilisates regarding differences from the reference medicines.

Espranor oral lyophilisate is a freeze-dried wafer which dissolves rapidly on the tongue. It is licensed for use in adults and adolescents over 15 years of age, as part of a medical, social and psychological treatment programme for addiction.

How is Espranor 2 mg and 8 mg oral lyophilisate used?

A single Espranor oral lyophilisate is placed whole on the tongue until dissolved. After administration, patients should avoid swallowing these medicines during the first 2 minutes, and should not eat or drink for at least 5 minutes.

In patients who are dependent on heroin or a short acting opioid, the first dose of Espranor should be taken at least 6 hours after the patient last used the opioid or when signs of withdrawal appear.

In patients who are dependent on methadone or a long acting opioid, the patient will not start treatment with Espranor until the daily dose of methadone is 30 mg a day or less. The first dose of Espranor should be taken when signs of withdrawal appear, but not less than 24 hours after a patient last used methadone.

A doctor will adjust the dose depending on the patient’s response to treatment.

Espranor 2 mg and 8 mg oral lyophilisates can only be obtained with a prescription from a healthcare professional.

For further information on how Espranor 2 mg and 8 mg oral lyophilisates are used, please see the Summaries of Product Characteristics and package leaflet available on the Medicines and Healthcare Products Regulatory Agency (MHRA) website.

How does Espranor 2 mg and 8 mg oral lyophilisate work?

Espranor contains the active ingredient buprenorphine, an opioid (narcotic) analgesic. When it is used for the treatment of patients addicted to opiate (narcotic) drugs, such as morphine or heroin, it acts as a substitute for these drugs and therefore aids the patient in withdrawing from them over a period of time.

What benefits of Espranor 2 mg and 8 mg oral lyophilisate has been shown in studies?

Because Espranor 2 mg and 8 mg oral lyophilisates are hybrid applications of Subutex 2 mg and 8 mg sublingual tablets and bioequivalence to the reference products have not been demonstrated, clinical studies have been provided for Espranor 2 mg and 8 mg oral lyophilisate to show the safety and efficacy of Espranor compared to Subutex 2 mg and 8 mg sublingual tablets in opioid dependent patients.

What are the possible side effects from Espranor 2 mg and 8 mg oral lyophilisate?

Like all medicines, Espranor 2 mg and 8 mg oral lyophilisate can cause side effects, although not everybody gets them.

The very common side effects with Espranor 2 mg and 8 mg oral lyophilisate (which may affect more than 1 in 10 people) are insomnia (inability to sleep), constipation, feeling or being sick (nausea), sweating, headache and drug withdrawal syndrome.

Common side effects with Espranor 2 mg and 8 mg oral lyophilisate (which may affect up to 1 in 10 people) are weight loss, swelling (hands and feet), tiredness, drowsiness, anxiety, nervousness, tingling, depression, decreased sexual drive, increase in muscle tension, abnormal thinking, increased tearing (watering eyes) or other tearing disorder, blurred vision, flushing, increased blood pressure, palpitations, widening of blood vessel, migraines, runny nose, sore throat and painful swallowing, increased cough, upset stomach or other stomach discomfort, diarrhoea, abnormal liver function, flatulence, vomiting, numbness of the tongue or mouth, rash, itching, hives, pain, joint pain, muscle pain, leg cramps (muscle spasm), difficulty in getting or keeping an erection, urine abnormality, abdominal pain, back pain, weakness, infection, chills, chest pain, fever, flu-like symptoms, feeling of general discomfort, accidental injury caused by loss of alertness or co-ordination, faintness and dizziness and drop in blood pressure on changing position from sitting or lying down to standing.

For the full list of all side effects reported with Espranor 2 mg and 8 mg oral lyophilisates, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Espranor 2 mg and 8 mg oral lyophilisate approved?

The MHRA decided that the benefits of Espranor 2 mg and 8 mg oral lyophilisates are greater than their risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Espranor 2 mg and 8 mg oral lyophilisate?

A Risk Management Plan (RMP) has been developed to ensure Espranor 2 mg and 8 mg oral lyophilisates are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics, package leaflet and outer labelling (carton) for Espranor 2 mg and 8 mg oral lyophilisates, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Espranor 2 mg and 8 mg oral lyophilisate

Malta, Sweden and the UK agreed to grant Marketing Authorisations for Espranor 2 mg and 8 mg oral lyophilisates on 22nd May 2015. Marketing Authorisations were granted in the UK on 22nd June 2015.

For more information about taking Espranor 2 mg and 8 mg oral lyophilisates, read the Patient Information Leaflet (PIL), or contact your doctor, pharmacist or nurse.

The full PAR for Espranor 2 mg and 8 mg oral lyophilisates follows this summary.

This summary was last updated in July 2015.

TABLE OF CONTENTS

I	Introduction	Page 6
II	Quality aspects	Page 6
III	Non-clinical aspects	Page 9
IV	Clinical aspects	Page 10
V	User consultation	Page 19
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 19
	Table of content of the PAR update	Page 24

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Espranor 2 mg and 8 mg oral lyophilisates (PL 00156/0364-0365; UK/H/5385/001-02/DC) are approvable. The products are prescription-only medicines (POM) indicated 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.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Malta and Sweden as Concerned Member States (CMSs). The applications were submitted 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, which were first authorised to Schering-Plough Limited (PL 00201/0241 & 0243) on 22nd December 1998. These reference licences underwent change of ownership procedures to the current Marketing Authorisation Holder, RB Pharmaceuticals Limited (PL 36699/0002-0003), on 29th September 2010.

The proposed and the reference products have different pharmaceutical forms. The proposed products are fast dissolving oral lyophilisates that disintegrate rapidly on the tongue and are absorbed *via* the oromucosal route.

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.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being hybrid medicinal products of originator products that have been in clinical use for over 10 years.

To support the applications three bioavailability (2 pilot and 1 pivotal) studies have been conducted, comparing the applicant's products with the reference products. In addition, the applicant has presented two Phase II safety studies that were conducted in the UK and India. The clinical studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing 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 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.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 207 – 22nd May 2015). After a subsequent national phase, the UK granted Marketing Authorisations (PL 00156/0364-0365) for these products on 22nd June 2015.

II QUALITY ASPECTS

II.1 Introduction

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

The excipients are gelatin, mannitol, aspartame (E951), mint flavour and anhydrous citric acid. Appropriate justification for the inclusion of each excipient has been provided.

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.

The only excipient used that contains material of animal or human origin is gelatin. Satisfactory documentation has been provided by the gelatin supplier(s) stating that the gelatin they provide complies with the criteria described in the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies'.

The finished products are packed in polyvinylchloride (PVC)/oriented polyamide (OPA)/aluminium (Al)/blisters with Al/polyethylene terephthalate (PET)/paper lidding with 7 or 28 oral lyophilisates, in a cardboard carton.

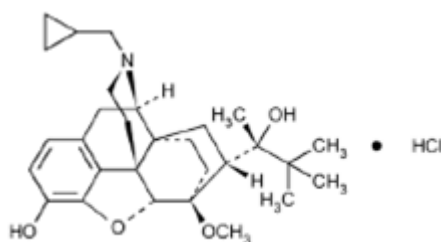
Not all pack sizes may be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups for approval before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 DRUG SUBSTANCE

INN: Buprenorphine Hydrochloride

Structure:



Molecular formula: $C_{29}H_{41}NO_4 \cdot HCl$

Molecular mass: 504.1 g/mol

Appearance: A white or almost white, crystalline powder.

Solubility: Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 percent), practically insoluble in cyclohexane.

Buprenorphine hydrochloride is the subject of a European Pharmacopoeia monograph.

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.

II.3 Medicinal Product Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered as hybrid medicinal products of the originator products Subutex 2 mg and 8 mg sublingual tablets (RB Pharmaceuticals Limited).

Suitable pharmaceutical development data have been provided for these applications.

Comparative dissolution and impurity profiles have been provided for these products and the UK originator products Subutex 2 mg and 8 mg sublingual tablets (RB Pharmaceuticals Limited).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, together with an appropriate account of the manufacturing process. The manufacturing process has been validated with commercial-scale batches and has shown satisfactory results.

Finished Product Specifications

The finished product specifications proposed are acceptable. The test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with a storage condition 'Store in the original package (blister) to protect from light and moisture' are set. These are satisfactory.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished products.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of Marketing Authorisations is recommended.

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 (ERA)

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 these products from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction

These applications have been 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 has 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.

In order to extrapolate further safety and efficacy data for Espranor, due to its higher bioavailability, the applicant has presented a Phase II study (MD2012/01XP-UK) that was conducted in the UK. In addition, a second Phase II study has also been conducted in India (MD2012/01XP-India).

Study RD216/24127 – Pilot Study

This is an open label, randomised, two way crossover pilot study comparing the bioavailability of the test product Buprenorphine 2 mg oral lyophilisate (Cardinal Health Ltd) with the reference product, Subutex 2 mg sublingual tablets (Schering-Plough Ltd) in 6 healthy, adult subjects under fasting conditions.

The volunteers were randomised to receive a single dose of 2 mg orally of either the test product or the reference product. Each dose of study medication was administered following pre-medication with a 50 mg naltrexone tablet (Nalorex, Bristol-Myers Squibb Pharmaceuticals Ltd) given 1 hour prior to the study medication, swallowed with 200 ml of water.

Serum drug levels were followed for 120 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max} . The washout period between phases was sufficiently long at 14 days, based on a terminal half-life for buprenorphine of 20-24 hours.

Result

Parameter	Test	Reference	Ratio T/R %	90% CI
C_{max} (ng/ml)	2.22	1.79	124.44	95.76-161.71
AUC_{0-t}	11.48	10.75	106.80	41.37-275.74
AUC_{0-inf}	15.81	16.11	98.15	42.73-225.43

Study RD216/24401 – Pilot study

This is an open label, randomised, two way crossover pilot study comparing the bioavailability of the test product Buprenorphine 8 mg oral lyophilisate (Cardinal Health Ltd) with the reference product, Subutex 8 mg sublingual tablets (Schering-Plough Ltd) in 8 healthy, adult subjects under fasting conditions.

The volunteers were randomised to receive a single dose of 8 mg orally of either the test product or the reference product. Each dose of study medication was administered following pre-medication with a 50 mg naltrexone tablet (Nalorex, Bristol-Myers Squibb Pharmaceuticals Ltd) given 1 hour prior to the study medication, swallowed with 200 ml of water.

Serum drug levels were followed for 72 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max} . The washout period between phases was sufficiently long at 14 days, based on a terminal half-life for buprenorphine of 20-24 hours.

Results

Parameter	Test	Reference	Ratio T/R %	90% CI
C_{max} (ng/ml)	6.11	7.53	81.17	58.96-111.73
AUC_{0-t}	51.72	53.83	96.09	71.49-129.14
AUC_{0-inf}	59.74	60.97	97.99	71.08-135.10

Study RD216/24132 – Pivotal Study

This is an open label, randomised, two way crossover study comparing the bioavailability of the test product Buprenorphine 8 mg oral lyophilisate (Cardinal Health Ltd) with the reference product, Subutex 8 mg sublingual tablets (Schering-Plough Ltd) in 36 healthy, adult subjects under fasting conditions.

The volunteers were randomised to receive a single dose of 8 mg orally of either the test product or the reference product. Each dose of study medication was administered

following pre-medication with a 50 mg naltrexone tablet (Nalorex, Bristol-Myers Squibb Pharmaceuticals Ltd) given 1 hour prior to the study medication, swallowed with 200 ml of water.

Serum drug levels were followed for 72 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max} . The washout period between phases was sufficiently long at 14 days, based on a terminal half-life for buprenorphine of 20-24 hours. This was confirmed with all pre-dose plasma levels being below the level of quantitation in both Periods.

Results

Parameter	Test	Reference	Ratio T/R %	90% CI
C_{max} (ng/ml)	5.77	4.45	129.51	118.94-141.02
AUC_{0-t}	26.71	19.42	137.50	122.15-154.78
AUC_{0-inf}	30.42	22.14	137.40	121.27-155.67

The test and reference products are not within conventional 90% CI limits of 80-125% in any of the measured parameters in the above studies. The test product is more available than the reference: plasma concentrations were higher, occurred later and overall exposure was higher in the test product.

The proposed products are not bioequivalent to the reference products, Subutex sublingual tablets. It has been demonstrated that the proposed products can be expected to achieve plasma concentrations of buprenorphine well in excess of those for the reference products. Therefore, it is reasonable to assume that these plasma levels will be more than sufficient to achieve efficacy in the requested indications.

Biowaiver

In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4 the Applicant requests a biowaiver to permit the extrapolation of the results from the pivotal 8 mg bioequivalence study to the 2 mg tablet strength based on the following:

1. The pharmaceutical products are manufactured by the same manufacturer and process
2. The drug input has been shown to be linear over the therapeutic dosage range
3. The qualitative composition of the different strengths is the same
4. The ratio between amounts of drug substance and excipients is the same
5. The dissolution profile is similar under identical conditions for the 2 mg tablet and the 8 mg batch used in the bioequivalence study.

Although bioequivalence has not been demonstrated, the justification for biowaiver can be accepted.

IV.3 Clinical Safety

Phase II study (MD2012/01XP)

A Phase II, randomised, single centre, open-label, two-arm study to determine the safety and efficacy of Buprenorphine Oral Lyophilisate (Espranor) in comparison with Buprenorphine Sublingual tablets (Subutex, reference product), in opioid dependent patients.

Primary objective

The primary objective of this study was to establish the safety profile of Espranor compared to Subutex.

Secondary objectives

1. Establish the pharmacokinetic (PK) profile in terms of time to maximum concentration (T_{max}) and maximum concentration (C_{max}) for Espranor and Subutex
2. Measure the disintegration and disappearance of Espranor and Subutex from the mouth under normal administration conditions
3. Establish the suitability of the recommended initiation dose (2 to 4 mg) and maintenance doses (up to 24 mg) of Espranor in opioid-dependent subjects.

Exploratory objective

The exploratory objective was to compare the dose requirements of Subutex versus Espranor.

36 subjects were to be randomised into the Maintenance Period in a 2:1 treatment. All subjects in this study who received at least 1 dose of study medication were analysed. Treatment was received for up to 29 days; Titration Period (7 days; Days 1 to 7), Maintenance Period (7 days; Days 8 to 14) and Extension Period (13 to 15 days; Days 27 to 29).

Espranor 2 mg and 8 mg oral lyophilisate was to be administered oro-mucosally (on the tongue). Titration of Espranor 2 mg and 8 mg oral lyophilisate was to be started with an initial dose of 2 to 4 mg/day, with additional doses up to an additional maximum of 4 mg on the first day if required based on clinical evaluation, and then increased by 2 to 6 mg/day based on subject response. Espranor 2 mg and 8 mg oral lyophilisate could be titrated up to a maximum dose of 24 mg/day and a maximum dose of 24 mg/day could be administered during the Maintenance Period.

Subutex was to be taken sublingually and retained until disintegration. Titration of Subutex was to be started with an initial dose of 2 to 4 mg/day, with additional doses up to an additional maximum of 4 mg on the first day if required based on clinical evaluation, subject to conventional clinical practice, and then increased daily based on subject response. Subutex could be titrated up to a maximum dose of 32 mg/day and a maximum dose of 32 mg/day could be administered during the Maintenance Period.

Criteria for Evaluation:

Efficacy: Medication hold and dose adequacy (Likert) scales, OOWS (Objective Opioid Withdrawal Scale), SOWS (Subjective Opioid Withdrawal Scale), and study drug oral disintegration time

Safety: Respiratory rate (RR), pulse oximetry, oro-mucosal safety, urine drug screens for cocaine and amphetamine, and routine safety assessments including AEs, laboratory evaluations, physical examinations, vital signs, 12 lead ECGs, and pregnancy tests (where applicable).

Pharmacokinetic (PK): area under the curve from 0 to 3 hours (AUC_{0-3hr}), C_{max} , and T_{max} .

Results

There was no statistically significant difference in respiratory depression between Espranor and Subutex when comparing subject differences from Baseline (end of

titration period) to Maintenance Days 2 and 7 for SpO₂ (peripheral capillary saturation) < 90% events lasting ≥ 1 minute or duration of SpO₂ < 90% in either the 0 to 30 minute or 0 to 120 minute post-dose period. In addition, there were no statistically significant differences between Espranor and Subutex for either the mean respiration rate or mean categorical SpO₂% during the 0 to 60 minute post dose periods across assessment periods.

At the end of the Titration Period, the mean dose of buprenorphine was 10.8 mg ± 4.85 mg for Espranor (range: 2 mg to 20 mg) and 9.6 mg ± 4.27 mg for Subutex (range: 4 mg to 16 mg).

At Maintenance Day 7, the mean dose of buprenorphine was 10.7 mg ± 4.91 mg (range: 2 mg to 20 mg) in the Espranor 2 mg and 8 mg oral lyophilisate group and 9.6 mg ± 4.27 mg (range: 4 mg to 16 mg) in the Subutex group.

At the End of the Extension Period, the mean dose of buprenorphine was 10.5 mg ± 4.98 mg (range: 2 mg to 20 mg) in the Espranor 2 mg and 8 mg oral lyophilisate group and 10.2 mg ± 4.05 mg (range: 6 mg to 16 mg) in the Subutex group. Similarly, the time required to titrate to an effective dose was comparable across the Espranor 2 mg and 8 mg oral lyophilisate and Subutex groups, with 81.8% (18 of 22 subjects) and 90.9% (10 of 11 subjects) of subjects respectively requiring no further titration after Day 3.

Conclusion

There were no deaths or serious adverse events reported during the study. Administration of Espranor did not result in a higher risk of respiratory depression when compared to Subutex. Two Espranor subjects reported 3 events of oral hypaesthesia at 5-10 minutes after administration and then resolved within 20 minutes, 20 to 25 minutes and within an hour.

There were no major safety issues recorded during the study. However, a higher number of mild treatment-emergent adverse events (TEAEs) were reported in the Espranor group and mainly associated with withdrawal symptoms. The most commonly reported TEAEs in the Espranor group were symptoms commonly associated with opioid withdrawal (headache, arthralgia and rhinorrea), and oral hypoesthesia.

Espranor was shown to be as efficacious as Subutex in reducing cravings, holding subjects, and preventing withdrawal symptoms in subjects with an extended opioid dependency.

Phase II supportive study (MD2012/01XP-India)

A Phase II, randomised, multi-centric, open-label, two-arm study to determine the safety profile and establish the efficacy of Espranor (Buprenorphine oral lyophilisate) in comparison with Subutex (Buprenorphine hydrochloride, reference product), in opioid-dependent subjects.

Primary Objective

- The primary objective of this study was to establish the safety profile of Espranor 2 mg and 8 mg oral lyophilisate compared to Subutex.

Secondary Objectives

- The secondary objectives of this study were to:
 1. To determine the efficacy of Espranor 2 mg and 8 mg oral lyophilisate compared to Subutex in opioid dependent patients.
 2. Measure the disintegration and disappearance of Espranor 2 mg and 8 mg oral lyophilisate and Subutex from the mouth under normal administration conditions.
 3. Establish the suitability of the recommended initiation dose (2 to 4 mg) and maintenance doses (up to 24 mg) of Espranor 2 mg and 8 mg oral lyophilisate in opioid-dependent patients.

Exploratory Objective

The exploratory objective was to compare the dose requirements of Subutex versus Espranor 2 mg and 8 mg oral lyophilisate.

All subjects who met the eligibility criteria were initially stratified into non-regular and regular benzodiazepine users, and then 54 subjects were randomised in a 2:1 ratio Espranor: Subutex across both strata.

Following randomization, patients were titrated upwards, to an effective single daily dose of either;

- Espranor; starting dose 2-4 mg/day, increasing in 2-6 mg steps up to 24 mg/day
- OR
- Subutex; starting dose 2-4 mg/day, increasing in 2-8 mg steps up to 32 mg/day, which would control withdrawal symptoms (observer and patient rating scales) and provides dose adequacy (Likert) scale of at least “adequately held”.

This period would last for 7 days. If patients were to be titrated to an effective dose before 7 days, they would be observed daily for the remainder of this period. However non-responders at the maximum titrated dose were to be withdrawn at the end of titration period.

Following titration the effective study dose was to be administered, for a Maintenance Period of 7 days. Treatment was received over 14 days: Titration Period (7 days; Days 1 to 7), and Maintenance Period (7 days; Days 8 to 14).

Statistical Methods

Statistical comparison of the efficacy of the 2 treatments during the Maintenance phase (Day 2 and Day 7) was assessed by determining the change in Likert, SOWS, and OOWS Score from Baseline (end titration).

Statistical comparison of the safety of the 2 treatments during the Maintenance Period (Days 2 and 7) regarding potential for respiratory depression potential was assessed by determining the change from Baseline (end of titration assessment).

Results

There was no statistically significant difference in respiratory depression between Espranor and Subutex when comparing subject differences from baseline (end of titration period) to Maintenance Days 2 and 7 for SpO₂% < 90% events lasting ≥ 1 minute or duration of SpO₂% < 90%, in either the 0 to 30 min, 0-120 min or 0-180 minutes post-dose period. There were no statistically significant differences between

Espranor and Subutex for either the mean respiration rate or mean categorical SpO₂% during the 0-60 min post-dose periods across assessment periods.

Both the respiratory rate and oxygen saturation results were comparable in both groups at all times during the study. There were no severe adverse events (AEs), TEAEs resulting in withdrawal, serious adverse events (SAEs), or deaths reported in either the Espranor or Subutex arms. The number of subjects with TEAEs was marginally higher in the Espranor arm as compared to the Subutex arm and the proportion of subjects having mild TEAEs was marginally higher in the Espranor arm as compared to the Subutex arm. However the proportion of subjects having moderate TEAEs was slightly higher in the Subutex arm as compared to the Espranor arm. All patients with AEs recovered completely in both the arms.

As this study was conducted in India, it can only be considered as supportive since treatment practice, patient population, support network, type of addiction etc. can be different compared to UK. However, the safety results were similar to the UK study and no major issues were found.

IV.4 Clinical efficacy

In the two Phase II safety studies (MD2012/01XP and MD2012/01XP-India) 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 Risk Management Plan (RMP)

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.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Abuse of buprenorphine	Ensure awareness through SmPC	None
Physical dependence	Ensure awareness through SmPC	None
Hepatitis/ liver necrosis/ hepatic impairment	Ensure awareness through SmPC	None
Respiratory depression	Ensure awareness through SmPC	Educational material
Overdose	Ensure awareness through SmPC	Educational material
Neonatal Abstinence Syndrome	Ensure awareness through SmPC	None
Drowsiness	Ensure awareness through SmPC	None
Orthostatic hypotension	Ensure awareness through SmPC	None
Use in patients with renal insufficiency	Ensure awareness through SmPC	None
Diversion	Ensure awareness through SmPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with hypersensitivity to the active substance or any of the excipients	Ensure awareness through SmPC	None
Use in patients with asthma or respiratory insufficiency	Ensure awareness through SmPC	None
Use in patients with hepatic impairment	Ensure awareness through SmPC	None
Use in patients with acute alcoholism or delirium tremens	Ensure awareness through SmPC	None
Use in combination with other CNS depressants	Ensure awareness through SmPC	Educational material
Use in combination with CYP3A4 inhibitors	Ensure awareness through SmPC	None
Precipitated withdrawal in opioid-dependent patients	Ensure awareness through SmPC	None
Effect of reducing patients reactions and ability to drive	Ensure awareness through SmPC	None
Breastfeeding	Ensure awareness through SmPC	None
Misuse (injection/intranasal)	Ensure awareness through SmPC	None
Medication errors	Ensure awareness through SmPC	Educational material
Use in the paediatric population	Ensure awareness through SmPC	None
Effects on pregnancy and foetal development	Ensure awareness through SmPC	None
Use in patients with head injury, increased intracranial pressure, hypotension, prostatic hypertrophy or urethral stenosis	Ensure awareness through SmPC	None

IV.6 Conclusion

The grant of Marketing Authorisations is recommended.



V. User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

The package leaflet meets the criteria for readability as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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.

<p>Espranor™ 2mg oral lyophilisate Buprenorphine Martindale Pharma</p> <p>Lot: Exp:</p> 	<p>Espranor™ 2mg oral lyophilisate Buprenorphine Martindale Pharma</p> <p>Lot: Exp:</p> 
 <p>Espranor™ 2mg oral lyophilisate Buprenorphine Martindale Pharma</p> <p>Lot: Exp:</p>	 <p>Espranor™ 2mg oral lyophilisate Buprenorphine Martindale Pharma</p> <p>Lot: Exp:</p>
<p>Martindale Pharma</p> <p><i>Peel foil at arrow</i> D02135</p>	<p>Espranor™ 2mg oral lyophilisate Buprenorphine Martindale Pharma</p> <p>Lot: Exp:</p> 
 <p>Espranor™ 2mg oral lyophilisate Buprenorphine Martindale Pharma</p> <p>Lot: Exp:</p>	 <p>Espranor™ 2mg oral lyophilisate Buprenorphine Martindale Pharma</p> <p>Lot: Exp:</p>






<p>Espranor™ 8mg oral lyophilisate Buprenorphine</p> <p>Martindale Pharma Lot: Exp:</p> 	<p>Espranor™ 8mg oral lyophilisate Buprenorphine</p> <p>Martindale Pharma Lot: Exp:</p> 
<p> Espranor™ 8mg oral lyophilisate Buprenorphine</p> <p>Martindale Pharma Lot: Exp:</p>	<p> Espranor™ 8mg oral lyophilisate Buprenorphine</p> <p>Martindale Pharma Lot: Exp:</p>
<p>Martindale Pharma</p> <p><i>Peel foil at arrow</i> D02136</p>	<p>Espranor™ 8mg oral lyophilisate Buprenorphine</p> <p>Martindale Pharma Lot: Exp:</p> 
<p> Espranor™ 8mg oral lyophilisate Buprenorphine</p> <p>Martindale Pharma Lot: Exp:</p>	<p> Espranor™ 8mg oral lyophilisate Buprenorphine</p> <p>Martindale Pharma Lot: Exp:</p>

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached Y/N (version)