Buprenorphine 0.4mg Sublingual Tablets
Buprenorphine 2mg Sublingual Tablets
Buprenorphine 8mg Sublingual Tablets
PL 00240/0347
PL 00240/0354
PL 00240/0355
UKPAR

TABLE OF CONTENTS

Lay summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 16
Summary of product characteristics Page 17
Patient information leaflet Page 38
Labelling Page 41
BUPRENORPHINE 0.4MG SUBLINGUAL TABLETS

BUPRENORPHINE 2MG SUBLINGUAL TABLETS

BUPRENORPHINE 8MG SUBLINGUAL TABLETS

PL 00240/0347

PL 00240/0354-5

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Buprenorphine 0.4mg, 2mg and 8mg Sublingual Tablets (Product Licence numbers: PL 00240/0347, PL 00240/0354 and PL 00240/0355).

Buprenorphine is used for the treatment of patients addicted to opiate (narcotic) drugs, such as morphine and heroin. It acts as a substitute for these drugs and, therefore, helps the patient to withdraw from them over a period of time. If treatment is stopped abruptly, withdrawal symptoms may occur.

These tablets are described as sublingual. This means that the tablet should be placed under the tongue and kept there until fully dissolved, which usually occurs within 5 to 10 minutes.

Buprenorphine 0.4mg, 2mg and 8mg Sublingual Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
BUPRENORPHINE 0.4MG SUBLINGUAL TABLETS
BUPRENORPHINE 2MG SUBLINGUAL TABLETS
BUPRENORPHINE 8MG SUBLINGUAL TABLETS

PL 00240/0347
PL 00240/0354-5

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>8</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>9</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>15</td>
</tr>
</tbody>
</table>
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Buprenorphine 0.4mg, 2mg and 8mg Sublingual Tablets (PL 00240/0347, PL 00240/0354 and PL 00240/0355) to Thornton & Ross Ltd on 16 August 2010. These medicines are only available on prescription.

The applicant claims that Buprenorphine 0.4mg, 2mg and 8mg Sublingual Tablets are generic versions of Subutex 0.4mg, 2mg and 8mg, marketed by Schering Plough and first licensed in France on 31 July 1995. The UK reference product used in the bioequivalence study is Subutex 8 mg, which was first licensed in the UK to Schering-Plough Ltd on 22 December 1998 and is now licensed to RB Pharmaceuticals Limited (PL 36699/0003) following a change of ownership on 29 September 2010. The legal basis of these applications is acceptable as the ten year rule is complied with.

Buprenorphine is an opioid partial agonist/antagonist which attaches itself to the \( \mu \) (mu) and \( \kappa \) (kappa) receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible link with the \( \mu \) receptors which, over a prolonged period, minimises the need of the addicted patient for drugs. During clinical pharmacologic studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: BUPRENORPHINE HYDROCHLORIDE

Chemical names: 
[5α, 7α(S)]-17(cyclopropylmethyl)- α-(1,1-dimethyllethyl)-4,5-epxy-18,19-dihydr-3-hydroxy-6-methoxy- α-methyl-6,14-ethanomorphinan-7-methanol hydrochloride
21cyclopropyl-7 α-[S)-1-hydroxy-1, 2, 2-trimethylpropyl]-6,14-endo-ethano6, 7, 8, 14-tetrahydrooripavine

Structure

The molecule contains 7 chiral centres
Molecular formula: C_{29}H_{41}NO_{4},HCl
Molecular weight: 504.1

General Properties
A white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane.

The method of manufacture of buprenorphine hydrochloride is appropriate.

The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active buprenorphine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period.

DRUG PRODUCT

Composition
The product excipients are lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous, sodium citrate and magnesium stearate. The 0.4 mg tablets
also contain silica colloidal anhydrous and talc. Satisfactory certificates of analysis have been provided for all excipients. All excipients are Ph Eur and were tested in line with their Ph Eur monographs. There were no novel excipients used and no overages.

Lactose monohydrate is the only material of animal origin. The lactose manufacturer has confirmed that the milk used is sourced from healthy animals in the same condition as milk collected for human consumption and has provided confirmation that the lactose is prepared in accordance with the relevant requirements laid down in EMEA/410/01/rev 02.

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable tablets that contain qualitatively and quantitatively the same active ingredient as Subutex 0.4mg, 2mg and 8mg, and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications. A satisfactory account of the pharmaceutical development has been provided. Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each tablet strength. The results are satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

Buprenorphine 0.4mg Sublingual Tablets are stored in PVC/Aluminium blister packs and Buprenorphine 2mg and 8mg Sublingual Tablets are stored in PVC/PVDC/Aluminium blister packs. For all three tablets strengths seven tablets are included per carton.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. This medicinal product does not require any special storage conditions.

**Product literature**

All product literature (SPCs, PIL and labelling) are satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and
organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
INDICATIONS
These products should be used for the following:

“substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatment”

The indications for these products are satisfactory.

DOSE & DOSE SCHEDULE
The following dose schedule is recommended when taking this product:

“Treatment with Buprenorphine Sublingual Tablets is intended for use in adults and children age 16 years or over who have agreed to be treated for addiction. When initiating treatment the physician should be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients. Buprenorphine binds to the µ and κ opiate receptors. Administration is sublingual. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug. The tablet should be kept under the tongue until dissolved which usually occurs within 5 to 10 minutes. Induction therapy: the initial dose is from 0.8mg to 4mg, administered as a single daily dose.

. for opioid-dependent drug addicts who have not undergone withdrawal: one dose of Buprenorphine Tablets administered sublingually at least 4 hours after the last use of the opioid, or when the first signs of craving appear.

. for patients receiving methadone: before beginning Buprenorphine therapy, the dose of methadone should be reduced to a maximum of 30mg/day. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

- Dosage adjustment and maintenance: the dose of Buprenorphine should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 32 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient.

- Dosage reduction and termination of treatment: after a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose; when deemed appropriate, treatment may be discontinued in some patients. The availability of the sublingual tablet in doses of 0.4 mg, 2 mg and 8 mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.”

The posology for these products is satisfactory.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Buprenorphine is a semi-synthetic derivative of the naturally-occurring morphine alkaloid thebaine. It is a mixed opioid agonist-antagonist, acting mainly as a partial
agonist at \( \mu \) (mu) opiate receptors, with some antagonist activity at \( \kappa \) (kappa) opiate receptors of the brain.
At low doses buprenorphine produces analgesia and other effects on the central nervous system that are qualitatively similar to those of morphine.
At higher doses, the agonist effects of buprenorphine plateau and it begins to behave more like an antagonist, limiting its maximal analgesic effect and respiratory depression. This "ceiling effect" confers a beneficial safety profile with a low level of physical dependence and only mild withdrawal symptoms on cessation of prolonged treatment. The ceiling effect on feelings of euphoria may limit the abuse potential of the drug. As a result, buprenorphine has been used as a substitution treatment for opioid drug dependence.
The activity of buprenorphine in opioid maintenance treatment is attributed to its slowly reversible link with the \( \mu \) receptors which, over a prolonged period, minimises the need of the addicted patient for opioid drugs.

**Pharmacokinetics**
Oral doses of buprenorphine undergo extensive first-pass metabolism by N-dealkylation and glucuroconjugation in the small intestine. Peak plasma concentrations of buprenorphine are achieved approximately 90 minutes after sublingual administration. Following absorption, buprenorphine shows rapid distribution and a half-life of 2-5 hours. The result of a study in six healthy volunteers indicated that the bioavailability of sublingual buprenorphine is about 30% and those sublingual holding times between three and five minutes were associated with equivalent effects.
Buprenorphine has a large volume of distribution and is about 96 % bound to plasma proteins.
Buprenorphine crosses the placenta and passes into breast milk.
Buprenorphine undergoes oxidative metabolism by 14-N-dealkylation to N-desalkyl-buprenorphine (norbuprenorphine) via cytochrome P450 CYP3A4 and by glucuroconjugation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is a \( \mu \) (mu) agonist with weak intrinsic activity at opioid receptors.
Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase of 20-25 hours. This is due partly to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative and partly to the highly lipophilic nature of the molecule.
Buprenorphine is essentially eliminated in the faeces by biliary excretion of its glucuroconjugated metabolites (80 %). The remainder is eliminated in the urine.

**Special populations**
Buprenorphine should be used with caution in patients with renal insufficiency as 20 % of the administered dose is eliminated via the kidneys.
Since CYP3A activity may be decreased in patients with hepatic insufficiency, it is possible that the metabolism of buprenorphine will be altered. Buprenorphine should therefore be used with caution in patients with hepatic insufficiency.

**Bioequivalence**
Two bioequivalence studies were conducted in support of these applications; one using the 0.4 mg strength tablets and the other using the 8 mg strength tablets. The 0.4 mg tablets differ somewhat compared to the other strengths in terms of formulation
and method of manufacture, therefore, a separate study on this strength was performed. Absence of a bioequivalence study for the 2 mg sublingual tablets can be considered justified due to the fact that the 2 mg and 8 mg strength tablets are quantitatively proportional, have linear kinetics, have similar dissolution profiles and the same manufacturer and manufacturing processes. Partial biowaiver to the 2 mg strength has been justified by reference to section 5.4 of the Note for guidance on bioequivalence and bioavailability (CPMP/EWP/QWP/1401/98).

There is no specific information on any food recommendation in the originators product information. From this perspective, a fasting study is considered acceptable.

The bioequivalence studies that were carried out are described as follows:

(1) Randomised, open label, two-way crossover, two-sequence, single dose bioequivalence study of Buprenorphine Hydrochloride Sublingual Tablets 0.4 mg in normal, healthy, adult, male human subjects under fasting conditions.

**Study design**

All 30 of the subjects were no-smokers or moderate smokers (less than 5 cigarettes a day) for at least 3 months. In order to diagnose subjects who were physically opioid dependent or are intolerant of naltrexone, a naltrexone challenge test (50 mg) was performed on Day 1, prior to administration of buprenorphine in each period. Subjects who passed the naltrexone challenge on Day 1 were given a 100 mg dose of naltrexone approximately 3 hours prior the administration of buprenorphine.

Subjects received each treatment (test product Buprenorphine 0.4 mg/reference product Subutex 0.4 mg) on one occasion.

Blood samples were collected from each volunteer in the 60 hours after dosing and plasma concentrations of buprenorphine and its metabolite, norbuprenorphine, were assayed.

A total of 29 subjects completed the study and were evaluable for bioavailability (one subject left the study, due to a failed urine drug screen at Period 2 check-in).

The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and Cmax. This is satisfactory. The duration of sampling following dosing was sufficient for accurate estimation of AUCt, AUCinf and Cmax and the washout period of 21 days was sufficient to prevent carry-over effect.

Analysis of variance (ANOVA) was performed on the in-transformed AUC0-t, AUCinf and Cmax.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th></th>
<th>Parent drug</th>
<th>Active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.96 (0.86-1.06)</td>
<td>1.01 (0.95-1.08)</td>
</tr>
<tr>
<td>AUCt (ng.h/mL)</td>
<td>0.95 (0.87-1.04)</td>
<td>1.06 (0.98-1.14)</td>
</tr>
<tr>
<td>AUC∞ (ng.h/mL)</td>
<td>0.95 (0.87-1.04)</td>
<td>1.22 (1.08-1.37)</td>
</tr>
</tbody>
</table>
The 90% CI for the mean ratios of AUC_{\text{inf}}, \text{AUC}_t \text{ and } \text{Cmax} \text{ for the test/reference were within the acceptance criteria of } 80-125\%. \text{ The two formulations may, therefore, be considered to be bioequivalent under fasting conditions.}

(2) Randomized, open label, two-sequence, two-treatment, two-period, crossover, single dose bioequivalence study of Buprenorphine Hydrochloride Sublingual Tablets 8 mg in normal, healthy, adult, male human subjects under fasting conditions.

**Study design**

The subjects were confined in the facility approximately 19 hours before dosing until at least 48 hours post-dose during each period. In order to diagnose the subjects who were physically opioid dependent or were intolerant to Naltrexone, a Naltrexone Challenge Test was performed (subjects were administered one Naltrexone Hydrochloride Tablets USP 50 mg with 240 ml of water at approximately 15 hours prior to dosing of Buprenorphine) one day prior to the respective day of dosing for Buprenorphine in each period. After an overnight fast of at least 10 hours, subjects who could tolerate the Naltrexone Challenge test (i.e. subjects with non-opioid tolerance) done on day -1, were administered 100 mg of Naltrexone (two Naltrexone Hydrochloride Tablets USP 50 mg) with 240 mls of water in the morning of the dosing day in each period (approximately 3 hours prior to the administration of Buprenorphine tablets).

The subjects, who could tolerate the 100 mg dose of Naltrexone, were administered with a single dose of the test or the reference product sublingually at ambient temperature in each period as per the randomization schedule. Subjects who could not tolerate the 100 mg dose of Naltrexone, were not administered the Buprenorphine tablet.

Forty-eight (40+8 standby subjects) subjects were enrolled in the study. A total of 35 subjects completed the clinical phase of the study successfully. Plasma samples of 35 subjects, who completed the clinical phase of the study, were analyzed.

The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and Cmax. This is satisfactory. The duration of sampling following dosing was sufficient for accurate estimation of \text{AUC}_t, \text{AUC}_{\text{inf}} \text{ and } \text{Cmax} \text{ and the washout period of } 21 \text{ days was sufficient to prevent carry-over effect.}

ANOVA was performed on log transform and pharmacokinetic parameters Cmax, \text{AUC}_{t-} \text{ and } \text{AUC}_{\text{inf-r}}. \text{ To conclude bioequivalence, two one sided 90\% confidence intervals were calculated for test by reference ratio of geometric least square mean of } C_{\text{max}}, \text{AUC}_{t-} \text{ and } \text{AUC}_{\text{inf-r}}.

Results:
Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals. The 90% confidence intervals for test/reference lie within the acceptance criteria of 80-125%.

Safety
No serious adverse events were experienced during the study. A total of 36 AEs (19 after administration of Naltrexone but prior to Buprenorphine dosing and 17 events after administration of Buprenorphine) were reported.

The 90% CI for the mean ratios of AUCinf, AUCt and Cmax for the test/reference were within the acceptance criteria of 80-125%. The two formulations may therefore be considered to be bioequivalent under fasting conditions.

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Test Product (A)</th>
<th>Reference Product (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (11.76%)</td>
<td>2 (11.76%)</td>
</tr>
<tr>
<td>Giddiness</td>
<td>1 (5.88%)</td>
<td>2 (11.76%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1 (5.88%)</td>
<td>2 (11.76%)</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (5.88%)</td>
<td>1 (5.88%)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (17.65%)</td>
<td>1 (5.88%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (5.88%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8 (47.06%)</td>
<td>9 (52.94%)</td>
</tr>
</tbody>
</table>

CLINICAL SAFETY
No new data submitted

EXPERT REPORTS
The expert report is satisfactory and references the key literature.

PRODUCT LITERATURE
All product literature is medically satisfactory.

RECOMMENDATIONS
There are no clinical public health issues and the recommendation is to grant Marketing Authorisations for these preparations.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Buprenorphine 0.4mg, 2mg and 8mg Sublingual Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of buprenorphine is well established. The SPCs, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

SAFETY
No new safety data have been submitted with these applications. As the safety profile of buprenorphine is well-known, this is satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with buprenorphine. The risk benefit is therefore considered to be positive.
**BUPRENORPHINE 0.4MG SUBLINGUAL TABLETS**
**BUPRENORPHINE 2MG SUBLINGUAL TABLETS**
**BUPRENORPHINE 8MG SUBLINGUAL TABLETS**

**PL 00240/0347**

**PL 00240/0354-5**

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 5 February 2007</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 9 March 2007</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 16 November 2007 and the clinical dossier on 23 April 2008</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 2 September 2008 and the clinical dossier on 25 January 2010</td>
</tr>
<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 29/07/2009</td>
</tr>
<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 21 October 2009</td>
</tr>
<tr>
<td>7</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 11 March 2010 and the clinical dossier on 17 March 2010</td>
</tr>
<tr>
<td>8</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 15 April 2010 and the clinical dossier on 23 April 2010</td>
</tr>
<tr>
<td>9</td>
<td>The applications were determined on 16 August 2010</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Buprenorphine 0.4mg Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sublingual tablet contains buprenorphine hydrochloride 0.432mg equivalent to buprenorphine 0.4mg.
Excipient: 18.76mg of lactose per tablet.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Sublingual tablet
White, round, slightly biconvex uncoated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatment.

4.2 Posology and method of administration
Treatment with Buprenorphine Sublingual Tablets is intended for use in adults and children age 16 years or over who have agreed to be treated for addiction. When initiating treatment the physician should be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients. Buprenorphine binds to the \( \mu \) and \( \kappa \) opiate receptors.
Administration is sublingual. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug. The tablet should be kept under the tongue until dissolved which usually occurs within 5 to 10 minutes.

**Induction therapy**: the initial dose is from 0.8mg to 4mg, administered as a single daily dose.

- **for opioid-dependent drug addicts who have not undergone withdrawal**: one dose of Buprenorphine Tablets administered sublingually at least 4 hours after the last use of the opioid, or when the first signs of craving appear.

- **for patients receiving methadone**: before beginning Buprenorphine therapy, the dose of methadone should be reduced to a maximum of 30mg/day. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

- **Dosage adjustment and maintenance**: the dose of Buprenorphine should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 32 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient.
- **Dosage reduction and termination of treatment:** after a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose; when deemed appropriate, treatment may be discontinued in some patients. The availability of the sublingual tablet in doses of 0.4 mg, 2 mg and 8 mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

4.3 **Contraindications**

Hypersensitivity to buprenorphine or any other component of the tablet
- Children less than 16 years of age
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Acute alcoholism or delirium tremens
- Breast feeding

4.4 **Special warnings and precautions for use**

**Warnings**

Buprenorphine sublingual tablets are recommended only for the treatment of opioid drug dependence.
- The clinician should consider the risk of abuse and misuse (e.g. IV administration), particularly at the beginning of the treatment.
- **Respiratory Depression:** some cases of death due to respiratory depression have been reported, particularly when used in combination with benzodiazepines (see 4.5 Interaction with other medicaments and other forms of interaction) or when buprenorphine was not used according to labelling.
- **Hepatitis, hepatic events:** hepatic necrosis and hepatitis with jaundice, which generally have resolved favourably, have been reported in patients who use buprenorphine. Causality has not been clearly established. When a hepatic event is suspected and the causality is unknown, further evaluation is required. If Buprenorphine is suspected to be the cause of hepatic necrosis or jaundice, it must be discontinued as rapidly as the patient's clinical condition permits. All patients should have liver function tests performed at regular intervals. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by intravenous route. These hepatic injuries have mainly been observed at the high doses and may be promoted by viral infections particularly chronic C hepatitis, alcohol abuse, anorexia, and the concurrent use of other potentially hepatotoxic drugs.
- This product can cause opioid withdrawal symptoms if administered to an addicted patient less than 4 hours after the last use of the drug (see 4.2 Posology and method of administration.)
- This product can cause drowsiness, which may be exacerbated by other centrally acting agents, such as: alcohol, tranquillisers, sedatives, hypnotics (see 4.5 Interactions with other medicaments and other forms of interaction.)
- This product can cause orthostatic hypotension.
- Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce a low level of dependence.
- Athletes should be aware that this medicine may cause a positive reaction to “anti-doping tests.”
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Paediatric Use**

No data are available in children less than 16 years of age; therefore, Buprenorphine Tablets should not be used in children under the age of 16.

**Precautions for use**

This product should be used with care in patients with:
- asthma or respiratory insufficiency (cases of respiratory depression have been reported with buprenorphine);
- renal insufficiency (20% of the administered dose is eliminated by the renal route; thus, renal elimination may be prolonged);
- hepatic insufficiency (hepatic metabolism of buprenorphine may be altered).

**4.5 Interaction with other medicinal products and other forms of interaction**

Buprenorphine Sublingual Tablets should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine (see 4.7. Effects on the ability to drive vehicles or operate machinery.)

Buprenorphine should be used cautiously together with:
- Benzodiazepines: This combination may potentiate respiratory depression of central origin, with risk of death; therefore, dosages must be individually titrated and the patient monitored carefully. The risk of drug abuse should also be considered (see 4.4 Special warnings and special precautions for use).
- Other central nervous system depressants; other opioid derivatives (analgesics and antitussives); certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. This combination increases central nervous system depression.
- Monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.
- To date, no notable interaction has been observed with cocaine, the agent most frequently used by multi-drug abusers in association with opioids. A suspected interaction between buprenorphine injection and phenprocoumon, resulting in purpura, has been reported.

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_max and AUC of buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving Buprenorphine Tablets should be closely monitored and the dose of buprenorphine should be halved when starting treatment with ketoconazole.

Further titration of Buprenorphine Tablets should be made as clinically indicated. Although no data from clinical trials are available, the use of other inhibitors of CYP3A4 (e.g. gestodene, troleandomycin, the HIV protease inhibitors ritonavir, indinavir and saquinavir) may also increase exposure levels to buprenorphine and norbuprenorphine and a similar dose-reduction should be considered when initiating treatment.
The interaction of buprenorphine with CYP 3A4 inducers has not been investigated, therefore it is recommended that patients receiving Buprenorphine Tablets should be closely monitored if enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. Use of these medications may increase the metabolism of buprenorphine and the dose of buprenorphine should be increased appropriately if patients complain of decreased benefit from buprenorphine or if there is re-emergence of craving for illicit drugs.

4.6 Pregnancy and lactation
Studies in rats and rabbits have evidenced foetotoxicity including post-implantation loss. In addition, maternal oral administration at high doses during gestation and lactation resulted in a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.
In humans, there is currently not sufficient data to evaluate potential malformative or foetotoxic effects of buprenorphine when administered during pregnancy.
At the end of pregnancy, high doses, even for a short duration of time, may induce respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. Consequently, the use of buprenorphine is not recommended during pregnancy.

Breast-feeding
As evidenced in rats, buprenorphine has the potential to inhibit lactation or milk production. In addition, because buprenorphine passes into the mother's milk, breast-feeding is contra-indicated.

4.7 Effects on ability to drive and use machines
Buprenorphine Tablets may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants. Therefore, patients should be warned against driving or operating machinery (see 4.5 Interaction with other medicaments and other forms of interaction.)

4.8 Undesirable effects
The onset of side effects depends on the patient's tolerance threshold, which is higher in drug addicts than in the general population.
The symptoms most frequently observed with buprenorphine administration are:
- constipation
- headaches
- insomnia
- asthenia
- drowsiness
- nausea and vomiting
- fainting and dizziness
- orthostatic hypotension
- sweating
Other side effects that have been reported are:
- respiratory depression (see 4.4 Special warnings and special precautions for use, and 4.5 Interaction with other medicaments and other forms of interaction).
- hepatic necrosis and hepatitis (see 4.4 Special warnings and special precautions for use)
- hallucinations
Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have also been reported.
In case of IV misuse, local reactions, sometimes septic, and potentially serious acute hepatitis have been reported (see 4.4 “Special warnings and special precautions for use”).
In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

4.9 Overdose
In the event of accidental overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment: Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available. Use of an opioid antagonist (i.e. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.
The long duration of action of Buprenorphine Tablets should be taken into consideration when determining length of treatment needed to reverse the effects of an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
DRUGS USED IN OPIOID DEPENDENCE
(N: central nervous system)
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 pharmacologic studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.
5.2 Pharmacokinetic properties

Absorption
When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuron conjugation in the small intestine. The use of this medication by the oral route is therefore inappropriate. Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose-concentration relationship is linear, between 2 mg and 16 mg.

Distribution
The absorption of buprenorphine is followed by a rapid distribution phase and a half-life of 2 to 5 hours.

Metabolism and elimination
Buprenorphine is oxidatively metabolised by 14-N-dealkylation to N-desalkyl-buprenorphine (also known as norbuprenorphine) via cytochrome P450 CYP3A4 and by glucuron conjugation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity. Elimination of buprenorphine is bi- or tri- exponential, with a long terminal elimination phase of 20 to 25 hours, due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule. Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (80%), the rest being eliminated in the urine.

5.3 Preclinical safety data
Acute toxicity of buprenorphine was determined in the mouse and rat following oral and parenteral administration. The median lethal doses (LD50) in the mouse were 26, 94 and 261 mg/kg for intravenous, intraperitoneal and oral administration, respectively. The LD50 values in the rat were 35, 243, and 600 mg/kg for intravenous, intraperitoneal and oral administration, respectively.

When beagles were dosed continuously subcutaneously for one month, rhesus monkeys orally for one month and rats and baboons intramuscularly for six months, buprenorphine showed remarkably low tissue and biochemical toxicities.

From teratology studies in rats and rabbits, it was concluded that buprenorphine is not embryotoxic or teratogenic, and it does not have any marked effects on weaning potential. There were no adverse effects on fertility or general reproductive function in rats, although at the highest intramuscular dose (5mg/kg/day) the mothers experienced some difficulty in parturition and there was a high neonatal mortality.

Minimal to moderate hyperplasia of the bile duct with associated peribiliary fibrosis occurred in dogs following 52 weeks of oral dosing of 75mg/kg/day.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
mannitol
maize starch
povidone K30
citric acid anhydrous
sodium citrate
magnesium stearate
Silica colloidal anhydrous
Talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
7 tablets in PVC/Aluminium blister packs

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Thornton & Ross Ltd
Linthwaite
Huddersfield
West Yorkshire
HD7 5QH
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 00240/0347

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
16/08/2010

10 DATE OF REVISION OF THE TEXT
16/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Buprenorphine 2mg Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains buprenorphine hydrochloride 2.16mg equivalent to buprenorphine 2mg.
Excipient 47.84mg of lactose monohydrate per tablet.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Sublingual tablet
White, oval shaped, biconvex uncoated tablets with ‘2’ embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatment.

4.2 Posology and method of administration
Treatment with Buprenorphine Sublingual Tablets is intended for use in adults and children age 16 years or over who have agreed to be treated for addiction.
When initiating treatment the physician should be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients. Buprenorphine binds to the μ and κ opiate receptors. Administration is sublingual. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug. The tablet should be kept under the tongue until dissolved which usually occurs within 5 to 10 minutes.
Induction therapy: the initial dose is from 0.8mg to 4mg, administered as a single daily dose.
  . for opioid-dependent drug addicts who have not undergone withdrawal: one dose of Buprenorphine Tablets administered sublingually at least 4 hours after the last use of the opioid, or when the first signs of craving appear.
  . for patients receiving methadone: before beginning Buprenorphine therapy, the dose of methadone should be reduced to a maximum of 30mg/day. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.
- Dosage adjustment and maintenance: the dose of Buprenorphine should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 32 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient.
- Dosage reduction and termination of treatment: after a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose; when deemed appropriate, treatment may be discontinued in some patients. The availability of the sublingual tablet in doses
of 0.4 mg, 2 mg and 8 mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

4.3 Contraindications
Hypersensitivity to buprenorphine or any other component of the tablet
- Children less than 16 years of age
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Acute alcoholism or delirium tremens
- Breast feeding

4.4 Special warnings and precautions for use

**Warnings**
Buprenorphine sublingual tablets are recommended only for the treatment of opioid drug dependence.
- The clinician should consider the risk of abuse and misuse (e.g. IV administration), particularly at the beginning of the treatment.
- **Respiratory Depressed**: some cases of death due to respiratory depression have been reported, particularly when used in combination with benzodiazepines (see 4.5 Interaction with other medicaments and other forms of interaction) or when buprenorphine was not used according to labelling.
- **Hepatitis, hepatic events**: hepatic necrosis and hepatitis with jaundice, which generally have resolved favourably, have been reported in patients who use buprenorphine. Causality has not been clearly established. When a hepatic event is suspected and the causality is unknown, further evaluation is required.
- If Buprenorphine is suspected to be the cause of hepatic necrosis or jaundice, it must be discontinued as rapidly as the patient's clinical condition permits. All patients should have liver function tests performed at regular intervals. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by intravenous route. These hepatic injuries have mainly been observed at the high doses and may be promoted by viral infections particularly chronic C hepatitis, alcohol abuse, anorexia, and the concurrent use of other potentially hepatotoxic drugs.
- **This product can cause opioid withdrawal symptoms if administered to an addicted patient less than 4 hours after the last use of the drug** (see 4.2 Posology and method of administration.)
- **This product can cause drowsiness**, which may be exacerbated by other centrally acting agents, such as: alcohol, tranquillisers, sedatives, hypnotics (see 4.5 Interactions with other medicaments and other forms of interaction.)
- This product can cause orthostatic hypotension.
- Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce a low level of dependence.
- **Athletes should be aware that this medicine may cause a positive reaction to “anti-doping tests.”**

**Paediatric Use**
No data are available in children less than 16 years of age; therefore, Buprenorphine Tablets should not be used in children under the age of 16.
Precautions for use
This product should be used with care in patients with:
- asthma or respiratory insufficiency (cases of respiratory depression have been reported with buprenorphine);
- renal insufficiency (20% of the administered dose is eliminated by the renal route; thus, renal elimination may be prolonged);
- hepatic insufficiency (hepatic metabolism of buprenorphine may be altered).

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Buprenorphine Sublingual Tablets should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine (see 4.7. Effects on the ability to drive vehicles or operate machinery.)

Buprenorphine should be used cautiously together with:
- Benzodiazepines: This combination may potentiate respiratory depression of central origin, with risk of death; therefore, dosages must be individually titrated and the patient monitored carefully. The risk of drug abuse should also be considered (see 4.4 Special warnings and special precautions for use).
- Other central nervous system depressants; other opioid derivatives (analgesics and antitussives); certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. This combination increases central nervous system depression.
- Monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.
- To date, no notable interaction has been observed with cocaine, the agent most frequently used by multi-drug abusers in association with opioids.

A suspected interaction between buprenorphine injection and phenprocoumon, resulting in purpura, has been reported.

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving Buprenorphine Tablets should be closely monitored and the dose of buprenorphine should be halved when starting treatment with ketoconazole.

Further titration of Buprenorphine Tablets should be made as clinically indicated. Although no data from clinical trials are available, the use of other inhibitors of CYP3A4 (e.g. gestodene, troleandomycin, the HIV protease inhibitors ritonavir, indinavir and saquinavir) may also increase exposure levels to buprenorphine and norbuprenorphine and a similar dose-reduction should be considered when initiating treatment.

The interaction of buprenorphine with CYP 3A4 inducers has not been investigated, therefore it is recommended that patients receiving Buprenorphine Tablets should be closely monitored if enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Use of these medications may increase the metabolism of buprenorphine and
the dose of buprenorphine should be increased appropriately if patients complain of decreased benefit from buprenorphine or if there is re-emergence of craving for illicit drugs.

4.6 Pregnancy and lactation
Studies in rats and rabbits have evidenced foetotoxicity including post-implantation loss. In addition, maternal oral administration at high doses during gestation and lactation resulted in a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.
In humans, there is currently not sufficient data to evaluate potential malformative or foetotoxic effects of buprenorphine when administered during pregnancy.
At the end of pregnancy, high doses, even for a short duration of time, may induce respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. Consequently, the use of buprenorphine is not recommended during pregnancy.

Breast-feeding
As evidenced in rats, buprenorphine has the potential to inhibit lactation or milk production. In addition, because buprenorphine passes into the mother's milk, breast-feeding is contra-indicated.

4.7 Effects on ability to drive and use machines
Buprenorphine Tablets may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants. Therefore, patients should be warned against driving or operating machinery (see 4.5 Interaction with other medicaments and other forms of interaction.)

4.8 Undesirable effects
The onset of side effects depends on the patient's tolerance threshold, which is higher in drug addicts than in the general population.
The symptoms most frequently observed with buprenorphine administration are:
- constipation
- headaches
- insomnia
- asthenia
- drowsiness
- nausea and vomiting
- fainting and dizziness
- orthostatic hypotension
- sweating
Other side effects that have been reported are:
- respiratory depression (see 4.4 Special warnings and special precautions for use, and 4.5 Interaction with other medicaments and other forms of interaction).
- hepatic necrosis and hepatitis (see 4.4 Special warnings and special precautions for use)
- hallucinations
Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have also been reported.
In case of IV misuse, local reactions, sometimes septic, and potentially serious acute hepatitis have been reported (see 4.4 “Special warnings and special precautions for use”).
In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

4.9 Overdose
In the event of accidental overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.
Treatment: Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available. Use of an opioid antagonist (i.e. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.
The long duration of action of Buprenorphine Tablets should be taken into consideration when determining length of treatment needed to reverse the effects of an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
DRUGS USED IN OPIOID DEPENDENCE
(N: central nervous system)
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 pharmacologic studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.

5.2 Pharmacokinetic properties
Absorption
When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. The use of this medication by the oral route is therefore inappropriate.
Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose-concentration relationship is linear, between 2 mg and 16 mg.
Distribution
The absorption of buprenorphine is followed by a rapid distribution phase and a half-life of 2 to 5 hours.

Metabolism and elimination
Buprenorphine is oxidatively metabolised by 14-N-dealkylation to N-desalkyl-buprenorphine (also known as norbuprenorphine) via cytochrome P450 CYP3A4 and by glucuroconjugation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase of 20 to 25 hours, due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (80%), the rest being eliminated in the urine.

5.3 Preclinical safety data
Acute toxicity of buprenorphine was determined in the mouse and rat following oral and parenteral administration. The median lethal doses (LD₅₀) in the mouse were 26, 94 and 261 mg/kg for intravenous, intraperitoneal and oral administration, respectively. The LD₅₀ values in the rat were 35, 243, and 600 mg/kg for intravenous, intraperitoneal and oral administration, respectively.

When beagles were dosed continuously subcutaneously for one month, rhesus monkeys orally for one month and rats and baboons intramuscularly for six months, buprenorphine showed remarkably low tissue and biochemical toxicities.

From teratology studies in rats and rabbits, it was concluded that buprenorphine is not embryotoxic or teratogenic, and it does not have any marked effects on weaning potential. There were no adverse effects on fertility or general reproductive function in rats, although at the highest intramuscular dose (5mg/kg/day) the mothers experienced some difficulty in parturition and there was a high neonatal mortality.

Minimal to moderate hyperplasia of the bile duct with associated peribiliary fibrosis occurred in dogs following 52 weeks of oral dosing of 75mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
mannitol
maize starch
povidone K30
citric acid anhydrous
sodium citrate
magnesium stearate
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
3 years

6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions

6.5 **Nature and contents of container**
7 tablets per carton in PVC/PVDC/Aluminium blister packs

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Thornton & Ross Ltd
Linthwaite
Huddersfield
West Yorkshire
HD7 5QH
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00240/0354

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
16/08/2010

10 **DATE OF REVISION OF THE TEXT**
16/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Buprenorphine 8mg Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains buprenorphine hydrochloride 8.64mg equivalent to buprenorphine 8mg.
Excipient 191.36mg of lactose monohydrate per tablet.
For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Sublingual tablet
White, oval shaped, biconvex uncoated tablets with ‘8’ embossed on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Substitution treatment for opioid drug dependence within a framework of medical, social and psychological treatment.

4.2 Posology and method of administration
Treatment with Buprenorphine Sublingual Tablets is intended for use in adults and children age 16 years or over who have agreed to be treated for addiction.
When initiating treatment the physician should be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients. Buprenorphine binds to the µ and κ opiate receptors.
Administration is sublingual. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug. The tablet should be kept under the tongue until dissolved which usually occurs within 5 to 10 minutes.
Induction therapy: the initial dose is from 0.8mg to 4mg, administered as a single daily dose.
   for opioid-dependent drug addicts who have not undergone withdrawal: one dose of Buprenorphine Tablets administered sublingually at least 4 hours after the last use of the opioid, or when the first signs of craving appear.
   for patients receiving methadone: before beginning Buprenorphine therapy, the dose of methadone should be reduced to a maximum of 30mg/day. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.
- Dosage adjustment and maintenance: the dose of Buprenorphine should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 32 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient.
- Dosage reduction and termination of treatment: after a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose; when deemed appropriate, treatment may be discontinued in some patients. The availability of the sublingual tablet in doses
of 0.4 mg, 2 mg and 8 mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

4.3 Contraindications
Hypersensitivity to buprenorphine or any other component of the tablet
- Children less than 16 years of age
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Acute alcoholism or delirium tremens
- Breast feeding

4.4 Special warnings and precautions for use

Warnings
Buprenorphine sublingual tablets are recommended only for the treatment of opioid drug dependence.
- The clinician should consider the risk of abuse and misuse (e.g. IV administration), particularly at the beginning of the treatment.
- Respiratory Depression: some cases of death due to respiratory depression have been reported, particularly when used in combination with benzodiazepines (see 4.5 Interaction with other medicaments and other forms of interaction) or when buprenorphine was not used according to labelling.
- Hepatitis, hepatic events: hepatic necrosis and hepatitis with jaundice, which generally have resolved favourably, have been reported in patients who use buprenorphine. Causality has not been clearly established. When a hepatic event is suspected and the causality is unknown, further evaluation is required. If Buprenorphine is suspected to be the cause of hepatic necrosis or jaundice, it must be discontinued as rapidly as the patient's clinical condition permits. All patients should have liver function tests performed at regular intervals. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by intravenous route. These hepatic injuries have mainly been observed at the high doses and may be promoted by viral infections particularly chronic C hepatitis, alcohol abuse, anorexia, and the concurrent use of other potentially hepatotoxic drugs.
- This product can cause opioid withdrawal symptoms if administered to an addicted patient less than 4 hours after the last use of the drug (see 4.2 Posology and method of administration.)
- This product can cause drowsiness, which may be exacerbated by other centrally acting agents, such as: alcohol, tranquillisers, sedatives, hypnotics (see 4.5 Interactions with other medicaments and other forms of interaction.)
- This product can cause orthostatic hypotension.
- Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce a low level of dependence.
- Athletes should be aware that this medicine may cause a positive reaction to “anti-doping tests.”

Paediatric Use
No data are available in children less than 16 years of age; therefore, Buprenorphine Tablets should not be used in children under the age of 16.
Precautions for use
This product should be used with care in patients with:
- asthma or respiratory insufficiency (cases of respiratory depression have been reported with buprenorphine);
- renal insufficiency (20% of the administered dose is eliminated by the renal route; thus, renal elimination may be prolonged);
- hepatic insufficiency (hepatic metabolism of buprenorphine may be altered).

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Buprenorphine Sublingual Tablets should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine (see 4.7. Effects on the ability to drive vehicles or operate machinery.)

Buprenorphine should be used cautiously together with:
- Benzodiazepines: This combination may potentiate respiratory depression of central origin, with risk of death; therefore, dosages must be individually titrated and the patient monitored carefully. The risk of drug abuse should also be considered (see 4.4 Special warnings and special precautions for use).
- Other central nervous system depressants; other opioid derivatives (analgesics and antitussives); certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. This combination increases central nervous system depression.
- Monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.
- To date, no notable interaction has been observed with cocaine, the agent most frequently used by multi-drug abusers in association with opioids. A suspected interaction between buprenorphine injection and phenprocoumon, resulting in purpura, has been reported.

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving Buprenorphine Tablets should be closely monitored and the dose of buprenorphine should be halved when starting treatment with ketoconazole.

Further titration of Buprenorphine Tablets should be made as clinically indicated. Although no data from clinical trials are available, the use of other inhibitors of CYP3A4 (e.g. gestodene, troleandomycin, the HIV protease inhibitors ritonavir, indinavir and saquinavir) may also increase exposure levels to buprenorphine and norbuprenorphine and a similar dose-reduction should be considered when initiating treatment.

The interaction of buprenorphine with CYP 3A4 inducers has not been investigated, therefore it is recommended that patients receiving Buprenorphine Tablets should be closely monitored if enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. Use of these medications may increase the metabolism of buprenorphine and
the dose of buprenorphine should be increased appropriately if patients complain of decreased benefit from buprenorphine or if there is re-emergence of craving for illicit drugs.

4.6 Pregnancy and lactation
Studies in rats and rabbits have evidenced foetotoxicity including post-implantation loss. In addition, maternal oral administration at high doses during gestation and lactation resulted in a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.
In humans, there is currently not sufficient data to evaluate potential malformative or foetotoxic effects of buprenorphine when administered during pregnancy.
At the end of pregnancy, high doses, even for a short duration of time, may induce respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. Consequently, the use of buprenorphine is not recommended during pregnancy.

Breast-feeding
As evidenced in rats, buprenorphine has the potential to inhibit lactation or milk production. In addition, because buprenorphine passes into the mother's milk, breast-feeding is contra-indicated.

4.7 Effects on ability to drive and use machines
Buprenorphine Tablets may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants. Therefore, patients should be warned against driving or operating machinery (see 4.5 Interaction with other medicaments and other forms of interaction.)

4.8 Undesirable effects
The onset of side effects depends on the patient's tolerance threshold, which is higher in drug addicts than in the general population.
The symptoms most frequently observed with buprenorphine administration are:
- constipation
- headaches
- insomnia
- asthenia
- drowsiness
- nausea and vomiting
- fainting and dizziness
- orthostatic hypotension
- sweating
Other side effects that have been reported are:
- respiratory depression (see 4.4 Special warnings and special precautions for use, and 4.5 Interaction with other medicaments and other forms of interaction).
- hepatic necrosis and hepatitis (see 4.4 Special warnings and special precautions for use)
- hallucinations
Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have also been reported.

In case of IV misuse, local reactions, sometimes septic, and potentially serious acute hepatitis have been reported (see 4.4 “Special warnings and special precautions for use”).

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

4.9 Overdose

In the event of accidental overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

**Treatment:** Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available. Use of an opioid antagonist (i.e. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.

The long duration of action of Buprenorphine Tablets should be taken into consideration when determining length of treatment needed to reverse the effects of an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

**DRUGS USED IN OPIOID DEPENDENCE**

(N: central nervous system)

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 pharmacologic studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.

5.2 Pharmacokinetic properties

**Absorption**

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. The use of this medication by the oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose-concentration relationship is linear, between 2 mg and 16 mg.
**Distribution**
The absorption of buprenorphine is followed by a rapid distribution phase and a half-life of 2 to 5 hours.

**Metabolism and elimination**
Buprenorphine is oxidatively metabolised by 14-N-dealkylation to N-desalkyl-buprenorphine (also known as norbuprenorphine) via cytochrome P450 CYP3A4 and by glucuroconjugation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is a $\mu$ (mu) agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase of 20 to 25 hours, due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (80%), the rest being eliminated in the urine.

5.3 Preclinical safety data
Acute toxicity of buprenorphine was determined in the mouse and rat following oral and parenteral administration. The median lethal doses (LD$_{50}$) in the mouse were 26, 94 and 261 mg/kg for intravenous, intraperitoneal and oral administration, respectively. The LD$_{50}$ values in the rat were 35, 243, and 600 mg/kg for intravenous, intraperitoneal and oral administration, respectively.

When beagles were dosed continuously subcutaneously for one month, rhesus monkeys orally for one month and rats and baboons intramuscularly for six months, buprenorphine showed remarkably low tissue and biochemical toxicities.

From teratology studies in rats and rabbits, it was concluded that buprenorphine is not embryotoxic or teratogenic, and it does not have any marked effects on weaning potential. There were no adverse effects on fertility or general reproductive function in rats, although at the highest intramuscular dose (5mg/kg/day) the mothers experienced some difficulty in parturition and there was a high neonatal mortality.

Minimal to moderate hyperplasia of the bile duct with associated peribiliary fibrosis occurred in dogs following 52 weeks of oral dosing of 75mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
mannitol
maize starch
povidone K30
citric acid anhydrous
sodium citrate
magnesium stearate
6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
3 years

6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions

6.5 **Nature and contents of container**
7 tablets per carton in PVC/PVDC/Aluminium blister packs

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Thornton & Ross Ltd
Linthwaite
Huddersfield
West Yorkshire
HD7 5QH
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00240/0355

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**
16/08/2010

10 **DATE OF REVISION OF THE TEXT**
16/08/2010
Buprenorphine 0.4mg, 2mg, 8mg
Sublingual tablets

Patient information

Please read this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects become serious or you notice any side effects not listed in the leaflet please tell your doctor or pharmacist.

This leaflet informs you about:
1. What Buprenorphine 0.4mg, 2mg and 8mg Sublingual tablets are and what they are used for
2. Before you take Buprenorphine 0.4mg, 2mg and 8mg Sublingual tablets
3. How to take the tablets
4. Possible side effects
5. How to store the tablets
6. Further information

1. What Buprenorphine 0.4mg, 2mg and 8mg Sublingual tablets are and what they are used for
Buprenorphine 0.4mg, 2mg and 8mg Sublingual tablets contain buprenorphine hydrochloride equivalent to 0.4mg, 2mg or 8mg buprenorphine. Buprenorphine is one of a group of medicines used in opioid dependence. When it is used for the treatment of patients addicted to opiates (narcotic) drugs such as morphine and heroin, it acts as a substitute for these drugs and therefore aids the patient in withdrawing from them over a period of time. If treatment is stopped abruptly withdrawal symptoms can occur.
These tablets are described as 'sublingual'. This means that the tablet should be placed under the tongue and kept there until fully dissolved which usually occur within 5 to 10 minutes.

2. Before you take Buprenorphine 0.4mg, 2mg and 8mg Sublingual tablets
Buprenorphine 0.4mg, 2mg and 8mg Sublingual tablets should not be used:
- in children under the age of 16 years
- if you are allergic to buprenorphine or any of the other ingredients in this medicine
- if you have serious breathing problems
- if you have serious problems with your liver or if your doctor detects the development of such a problem during treatment
- if you are intoxicated due to alcohol or have delirium tremens (the shakes and hallucinations)
- if you are breast-feeding
- if you are pregnant (unless your doctor tells you to take it)

Tell your doctor if you have any of the following illnesses before treatment or develop them during treatment as your doctor may need to reduce your dose of this medicine or you may need extra treatment to control them:
- asthma or other breathing problems
- kidney disease

The tablets should be used exactly as prescribed by your doctor. Some people have died from respiratory failure (inability to breathe) whilst using benzodiazepines (medicines used to treat anxiety and sleep disorders) in combination with Buprenorphine and also when Buprenorphine was not used according to doctor’s instructions.
Therefore whilst you are being treated with this medicine do not use benzodiazepines unless they have been prescribed by your doctor.
Some cases of severe liver problems have occurred during treatment although they may not necessarily have been caused by these tablets. If you develop severe fatigue, have no appetite or if your skin or eyes look yellow tell your doctor immediately.
This medicine can cause withdrawal symptoms if you take it less than four hours after you use a narcotic (morphine, heroin or other related products).
This medicine can cause drowsiness, which may be made worse if you also drink alcohol or take tranquillisers or anti-anxiety drugs.
If you are drowsy do not drive or operate machinery.
The tablets may cause your blood pressure to drop suddenly causing you to feel dizzy if you get up too quickly from sitting or lying down.
Drug dependence may occur as a result of taking this medicine.
Athletes should be aware that this medicine may cause a positive reaction to anti-doping tests.
Are there any medicines that should not be taken at the same time as buprenorphine 0.4mg, 2mg and 8mg sublingual tablets?

You should not use benzodiazepines (medicines used to treat anxiety and sleep disorders) whilst you are taking this medicine unless they are prescribed by your doctor.

Strong painkillers and cough medicines containing codeine-related substances, certain anti-depressants including monoamine oxidase inhibitors, sedating antihistamines, sedatives, anti-anxiety drugs, certain drugs for high blood pressure and antipsychotic drugs may increase the effects of buprenorphine.

Ketoconazole a medicine used for the treatment of fungal infections can increase the effects of buprenorphine if both are taken at the same time. If you are taking ketoconazole or any of the following medicines: gestodene, trolderonimycin, the HIV protease inhibitors ritonavir, indinavir and saquinavir you should tell your doctor or pharmacist as they may need to reduce your dose of buprenorphine.

Also tell your doctor or pharmacist if you are taking any of the following medicines: phenobarbital, carbamazepine, phenytoin, rifampicin.

You will be closely monitored whilst you are taking these medicines at the same time as buprenorphine.

Be sure to tell your doctor if you are taking a blood thinning agent called phenprocoumon.

If you are taking any other medicines you should tell your doctor or pharmacist before you begin treatment with buprenorphine.

Do not drink alcohol or take medicines that contain alcohol whilst you are being treated with buprenorphine. Alcohol and certain other medicines (as listed above) increases the sedative effects of buprenorphine which can make driving or operating machinery hazardous.

This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take the tablets

The tablets are administered sublingually. This means that you must place the tablet under your tongue and allow it to dissolve which will take 5 to 10 minutes. This is the only effective and safe way the tablets should be taken. Do not chew or swallow them whole as this will make them ineffective.

Your doctor will tell you how many 0.4mg, 2mg or 8mg sublingual tablets to take and you should always follow his advice.

Adults and children over the age of 16 years: the initial dose is from 0.8 to 4mg administered once a day.

For drug addicts who have not undergone withdrawal: one dose of 0.4mg, 2mg or 8mg sublingual tablets at least four hours after the last use of the opioid (heroin) or when the first signs of craving appear.

For patients receiving methadone: before beginning treatment your doctor should reduce your dose of methadone to a maximum of 30mg a day.

These tablets may cause withdrawal symptoms in patients who are dependent on methadone.

During your treatment, your doctor may increase your dose to a maximum single daily dose of 32mg depending upon your response.

After a period of successful treatment, your doctor may gradually reduce your dose. Depending on your condition your dose may continue to be reduced under careful medical supervision until it is stopped altogether. Do not suddenly stop taking these tablets as this may cause withdrawal symptoms.

What to do in the case of overdose

You should contact your doctor immediately.

What to do if you forget to take your tablets

You should tell your doctor and follow his or her instructions.

4. Possible side effects

Like all drugs, these tablets may cause side effects. After your first dose you may suffer from some opioid withdrawal symptoms.

Other side effects which may occur are constipation, headaches, difficulty in sleeping, lack of energy or weakness, drowsiness, nausea and vomiting, feeling and dizziness, drop in blood pressure on changing position from sitting or lying down to standing, sweating.

Rarely the following have occurred: severe difficulty in breathing, liver problems, hallucinations.

If you think you are suffering from these or any other side effects you should tell your doctor.

Hypersensitivity (allergic) reactions have been reported. Symptoms may include skin rash, hives and itching. If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, swelling of the eyes, lips, tongue or throat) seek urgent medical help.

Drug dependence can occur as a result of taking this medicine.

5. How to store the tablets

Keep out of the reach and sight of children.

Do not use after the expiry date which is stamped on the container.

Medicines should not be disposed of via wastewater or household waste. Return any unused tablets to your pharmacist. These measures will help protect the environment.

6. Further Information

Each sublingual tablet contains buprenorphine hydrochloride equivalent to either 0.4mg, 2mg or 8mg buprenorphine base as the active ingredient along with the following inactive ingredients: Lactose monohydrate, mannitol, maize starch, potato dextrin K30, citric acid anhydrous, sodium citrate and magnesium stearate. Buprenorphine 0.4mg sublingual tablets also contain talc and silica colloidal anhydrous.

The sublingual tablets are available in cartons containing 7 tablets in a blister.

Marketing Authorisation Holder: The marketing authorisation holder is Thornton & Ross Ltd.

Manufacturer: The manufacturer is Thornton & Ross Ltd, Linthwaite, Huddersfield, HD7 5QH, UK

PL numbers: 00240/0347 0.4mg, 00240/0354 2mg, 06240/0355 8mg

Date of revision: June 2010

MSSS
LABELLING

Blister:

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548

Buprenorphine 0.4mg
Sublingual tablets
PL Holder: Thornton & Ross Ltd.
M548
Carton:
Blister:

<table>
<thead>
<tr>
<th>Buprenorphine 2mg Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
</tr>
<tr>
<td>M550</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 2mg Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
</tr>
<tr>
<td>M550</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 2mg Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
</tr>
<tr>
<td>M550</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 2mg Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
</tr>
<tr>
<td>M550</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 2mg Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
</tr>
<tr>
<td>M550</td>
</tr>
</tbody>
</table>
Carton:
Blister:

<table>
<thead>
<tr>
<th>Buprenorphine 8mg</th>
<th>Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
<td>M552</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 8mg</th>
<th>Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
<td>M552</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 8mg</th>
<th>Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
<td>M552</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 8mg</th>
<th>Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
<td>M552</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buprenorphine 8mg</th>
<th>Sublingual tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL Holder: Thornton &amp; Ross Ltd.</td>
<td>M552</td>
</tr>
</tbody>
</table>