Public Assessment Report

Decentralised Procedure

BUPRENORPHINE 2MG SUBLINGUAL TABLETS
BUPRENORPHINE 8MG SUBLINGUAL TABLETS

Procedure No: UK/H/1827/002-3/DC

UK Licence No: PL 20117/0119-20

MORNINGSIDE HEALTHCARE LIMITED
LAY SUMMARY

On 31st July 2009, the MHRA granted Morningside Healthcare Limited Marketing Authorisations (licences) for the medicinal products Buprenorphine 2mg and 8mg Sublingual Tablets (PL 20117/0119-20). These are prescription-only medicines (POM) that are used as a substitute (replacement) treatment in patients who are addicted to opioid drugs, such as heroin and morphine. The tablets prevent or reduce the unpleasant withdrawal symptoms experienced when an addict stops using opioid drugs.

The active ingredient, buprenorphine, belongs to a group of medicines called opioid analgesics (also known as “opiates” or “narcotics”). Opioid analgesics, such as morphine and diamorphine (heroin), are often subject to abuse, which can lead to dependence (addiction). If you are addicted to these drugs, you need a regular dose to feel “normal”. Otherwise you will develop withdrawal symptoms within a day or so of the last dose. Withdrawal symptoms include sweating, feeling hot and cold, runny eyes and nose, feeling or being sick, diarrhoea, stomach cramps, poor sleep and just feeling awful.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Buprenorphine 2mg and 8mg Sublingual Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

| **Product Name**   | Buprenorphine 2 mg Sublingual Tablets  
|                    | Buprenorphine 8 mg Sublingual Tablets |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substance** | Buprenorphine hydrochloride |
| **Form**            | Sublingual tablet |
| **Strength**        | 2mg and 8mg |
| **MA Holder**       | Morningside Healthcare Limited, 115 Narborough Road, Leicester LE3 0PA, United Kingdom |
| **Reference Member State (RMS)** | UK |
| **CMS**             | Ireland |
| **Procedure Number** | UK/H/1827/002-3/DC |
| **Timetable**       | Day 210 – 1st July 2009 |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Buprenorphine 2 mg Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2 mg of buprenorphine (as buprenorphine hydrochloride).
Excipient: Each tablet contains 20 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Sublingual tablet.

Off-white to brownish, oval, biplane tablets marked with “B2” 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 adolescents aged 16 years or over who have agreed to be treated for addiction.

When initiating buprenorphine 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.

Adults
Initiation therapy:

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medication (see section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).”

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 tablet(s) 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 appropriate, treatment deemed 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 of the excipients
- Children and adolescents 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. It is also recommended that that treatment is prescribed by a physician who ensures comprehensive management of the drug addicted patient(s)
- The clinician should consider the risk of abuse and misuse (e.g. IV administration), particularly at the beginning of the treatment.
- Diversion: Diversion refers to the introduction of Buprenorphine into the illicit market either by patients or by individuals who obtain the medicinal product through theft from patients or pharmacies. This diversion may lead to new addicts using Buprenorphine as the primary drug of abuse with the risk of overdose, spread of blood borne viral infections, respiratory depression and hepatic injury.
- The risk of serious adverse events such as overdose or treatment dropout is greater if a patient is under treated with Buprenorphine and continues to self medicate withdrawal symptoms with opioids, alcohol or other sedative-hypnotics in particular benzodiazepines.
- Dependence: Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type. Discontinuation of treatment may result in a withdrawal that may be delayed
- Respiratory Depression: some cases of death due to respiratory depression have been reported, particularly when used in combination with benzodiazepines (see Section 4.5) 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 Section 4.2).
- This product can cause drowsiness, which may be exacerbated by other centrally acting agents, such as: alcohol, tranquillisers, sedatives, hypnotics (see Section 4.5).
- 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 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).
Excipient:
This medicinal product 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 should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine (see Section 4.7).

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 $C_{\text{max}}$ and AUC of buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving buprenorphine should be closely monitored and the dose of buprenorphine should be halved when starting treatment with ketoconazole.

Further titration of buprenorphine 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 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

Pregnancy
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 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 Section 4.5).

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 Sections 4.4 and 4.5)
- hepatic necrosis and hepatitis (see Section 4.4)
- 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 Section 4.4).

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 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
Pharmacotherapeutic group: Drugs used in opioid dependence.
ATC code: N07 BC01

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.

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 (E421)
Maize starch
Citric acid, anhydrous
Sodium citrate
Povidone (Pasdone K29/32)
Magnesium stearate
Ascorbic acid
Edetic acid (EDTA)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 30°C.
Store in original package to protect from moisture.

6.5 Nature and contents of container
White opaque PVC/PVDC/Aluminium foil blisters with 7 tablets per blister.
Pack sizes: 7, 14, or 28 tablets per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORITY NUMBER(S)
Morningside Healthcare Limited
115 Narborough Road
Leicester LE3 0PA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0119

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
31/07/2009

10 DATE OF REVISION OF THE TEXT
31/07/2009
1 NAME OF THE MEDICINAL PRODUCT
Buprenorphine 8 mg Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 8 mg of buprenorphine (as buprenorphine hydrochloride).
Excipient: Each tablet contains 80 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Sublingual tablet.
Off-white to brownish, oval, biplane tablets marked with “B8” 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 adolescents aged 16 years or over who have agreed to be treated for addiction.

When initiating buprenorphine 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,

Adults
Initiation therapy:

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medication (see section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).”

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 tablet(s) 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 of the excipients
- Children and adolescents 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. It is also recommended that that treatment is prescribed by a physician who ensures comprehensive management of the drug addicted patient(s).
- The clinician should consider the risk of abuse and misuse (e.g. IV administration), particularly at the beginning of the treatment.
- Diversion: Diversion refers to the introduction of Buprenorphine into the illicit market either by patients or by individuals who obtain the medicinal product through theft from patients or pharmacies. This diversion may lead to new addicts using Buprenorphine as the primary drug of abuse with the risk of overdose, spread of blood borne viral infections, respiratory depression and hepatic injury.
- The risk of serious adverse events such as overdose or treatment dropout is greater if a patient is under treated with Buprenorphine and continues to self medicate withdrawal symptoms with opioids, alcohol or other sedative-hypnotics in particular benzodiazepines.
- Dependence: Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type. Discontinuation of treatment may result in a withdrawal that may be delayed
- Respiratory Depression: some cases of death due to respiratory depression have been reported, particularly when used in combination with benzodiazepines (see Section 4.5) 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 Section 4.2).
- This product can cause drowsiness, which may be exacerbated by other centrally acting agents, such as: alcohol, tranquillisers, sedatives, hypnotics (see Section 4.5).
- 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 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).
Excipient:
This medicinal product 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 should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine (see Section 4.7).

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 \( C_{\text{max}} \) and AUC of buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving buprenorphine should be closely monitored and the dose of buprenorphine should be halved when starting treatment with ketoconazole.

Further titration of buprenorphine 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 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

Pregnancy
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 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 Section 4.5).

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 Sections 4.4 and 4.5)
- hepatic necrosis and hepatitis (see Section 4.4)
- 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 Section 4.4).

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 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
Pharmacotherapeutic group: Drugs used in opioid dependence.
ATC code: N07 BC01

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 (E421)
- Maize starch
- Citric acid, anhydrous
- Sodium citrate
- Povidone (Plasdone K29/32)
- Magnesium stearate
- Ascorbic acid
- Edetic acid (EDTA)

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

24 months.
6.4 Special precautions for storage
Do not store above 30°C.
Store in original package to protect from moisture.

6.5 Nature and contents of container
White opaque PVC/PVDC/Aluminium foil blisters with 7 tablets per blister.
Pack sizes: 7, 14 or 28 tablets per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Morningside Healthcare Limited
115 Narborough Road
Leicester LE3 0PA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0120

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
31/07/2009

10 DATE OF REVISION OF THE TEXT
31/07/2009
Module 3

After your first dose, you may suffer from opioid withdrawal symptoms. This is more likely if buprenorphine is taken less than four hours after using an opioid (e.g. heroin).

Rare side effects: severe difficulty in breathing, hallucinations.
- Athletes should be aware that this medicine may cause a positive reaction to ‘antidoping tests’
- Drug dependence can occur as a result of taking this medicine.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Buprenorphine Sublingual Tablets

Keep out of the reach and sight of children.

Store your medicine in the original packaging to protect from moisture.

Do not store above 30°C

Do not use Buprenorphine Sublingual Tablets after the expiry date, which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Buprenorphine Sublingual Tablets contain:
- The active substance is buprenorphine (as buprenorphine hydrochloride). Each tablet contains 2 mg or 8 mg of buprenorphine.
- The other ingredients are lactose monohydrate, mannitol (E421), maize starch, dextrose (anhydrous), sodium citrate, povidone (plasdone K29/32), magnesium stearate, ascorbic acid and Edetate (EDTA).

What Buprenorphine Sublingual Tablets look like and the contents of the pack
Buprenorphine 2 mg Sublingual Tablets are off-white to brownish, oval, buprenorphine tablets marked with “B2” on one side.
Buprenorphine 8 mg Sublingual Tablets are off-white to brownish, oval, buprenorphine tablets marked with “B8” on one side.

Your medicine is available in blisters containing 7, 14, or 28 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Morningside Healthcare Limited
115 Narborough Road
Leicester
LE3 0PA
United Kingdom.

Manufacturer
SMB TECHNOLOGY S.A.
39 rue du Parc industriel
6900 Marche en Famenne
Belgium

This leaflet was last approved in June 2009

PACKAGE LEAFLET: INFORMATION FOR THE USER

Buprenorphine 2 mg and 8 mg Sublingual Tablets

(Buprenorphine)

Read all of 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, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Buprenorphine Sublingual Tablets are and what they are used for
2. Before you take Buprenorphine Sublingual Tablets
3. How to take Buprenorphine Sublingual Tablets
4. Possible side effects
5. How to store Buprenorphine Sublingual Tablets
6. Further information

1. What Buprenorphine Sublingual Tablets are and what they are used for

Buprenorphine belongs to a group of medicines called opioid analgesics (also known as "opiates" or "narcotics"). Opioid analgesics, such as morphine or diamorphine (heroin), are often subject to abuse, which can lead to dependence (addiction). If you are addicted to these drugs, you need a regular dose to feel "normal". Otherwise you will develop withdrawal symptoms within a day or so of the last dose. Withdrawal symptoms include sweating, feeling hot and cold, runny eyes and nose, feeling or being sick, diarrhoea, stomach cramps, poor sleep and just feeling awful.

Buprenorphine Sublingual Tablets are used as a substitution (replacement) treatment in patients who are addicted to opioid drugs such as heroin and morphine. The tablets prevent or reduce the unpleasant withdrawal symptoms experienced when addicts stop using opioid drugs.

Treatments with Buprenorphine Sublingual Tablets may form one aspect of a specialist support programme aimed at resolving opioid addiction.

The tablets are not to be used for pain relief purposes.

2. Before you take Buprenorphine Sublingual Tablets

Do not take Buprenorphine Sublingual Tablets
- If you are allergic (hypersensitive) to buprenorphine
- If you are allergic to any of the other ingredients in the tablets (these are listed in section 6, Further Information)
- If you have severe breathing problems
- If you have severe liver disease
- If you are an alcoholic or regularly drink large amounts of alcohol
- If you have delirium tremens (DTs), the shakes and hallucinations
- If you are breast-feeding (see the section ‘Pregnancy and breast-feeding’ below for more information)

Buprenorphine Sublingual Tablets must not be used by children or adolescents under 16 years old.

Take special care with Buprenorphine Sublingual Tablets
- Tell your doctor before taking these tablets:
  - If you have asthma or any other breathing problems
  - If you have any kidney problems
  - If you have any liver problems.
Taking other medicines
Tell your doctor if you are taking or have recently taken any of the following medicines as they may interact with Buprenorphine Sublingual Tablets.

The following medicines have sedative effects (make you feel sleepy/drowsy). These effects are increased if these medicines are taken while you are being treated with buprenorphine:

- Benzodiazepines (used for treatment of anxiety or sleep disorders) e.g. diazepam and temazepam: you should not take these medicines while you are taking buprenorphine, unless prescribed by your doctor because this combination can be fatal if the correct dose is not carefully determined.
- Barbiturates and other medicines used for the treatment of anxiety or sleep disorders.
- Other medicines containing opioid-related medicines e.g. codeine, dextropropoxyphene and morphine (used as strong painkillers and in some cough medicines).
- Medicines used for the treatment of depression, including medicines known as monoamine oxidase inhibitors (MAOIs) e.g. phenelzine.
- Antihistamine medicines (used for treatment of allergy and/or hay fever) e.g. promethazine and chlorphenamine.
- Medicines known as antipsychotics (used for the treatment of schizophrenia) e.g. chlorpromazine and haloperidol.
- Certain medicines for the treatment of high blood pressure (antihypertensives) e.g. clonidine.

If you are taking any of the following medicines, your doctor may need to prescribe a lower dose of buprenorphine:

- The antifungal medicine, ketoconazole.
- Medicines used to treat infections caused by viruses (antiviral agents) e.g. ritonavir, saquinavir and indinavir, which are used in the treatment of HIV.
- Oral contraceptive medicines containing gestodene.

- Certain medicines called macrolide antibiotics (used for the treatment of infections).
- If you are taking any of the following medicines, your doctor may need to prescribe a higher dose of buprenorphine:
  - Medicines used for the treatment of epilepsy e.g. phenobarbital, carbamazepine and phenytoin.
  - The anticoagulant medicine, warfarin (used for the treatment of tuberculosis).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Buprenorphine Sublingual Tablets with food and drink
These tablets should not be taken at the same time as food or drink. You should not drink alcohol or take any medicines that contain alcohol while taking buprenorphine sublingual tablets.

Pregnancy and breast-feeding
Before taking these tablets, tell your doctor if you are pregnant or trying to become pregnant. If you become pregnant during treatment with buprenorphine, tell your doctor straight away.

Since buprenorphine is passed into breast milk, you must not breast feed while taking this medicine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you feel drowsy while being treated with this medicine, you should not drive or operate machinery.

Important information about some of the ingredients of Buprenorphine Sublingual Tablets

Buprenorphine Sublingual Tablets contain lactose.

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Buprenorphine Sublingual Tablets

Always take Buprenorphine Sublingual Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The tablets are described as ‘sublingual’. This means that the tablet should be placed under the tongue and kept there until fully dissolved. Do not chew or swallow the tablets whole - the medicine will not work this way and you may get withdrawal symptoms. Do not take the tablets at the same time as food or drink.

Adults and adolescents aged 16 years and over:

- The usual starting dose is 0.8 mg to 4 mg daily.
  - If you are still taking opioids, the dose of buprenorphine must be taken at least 4 hours after the last use of the opioid or when the first signs of craving appear.
  - If you have been receiving methadone, your doctor should reduce the dose to no more than 30 mg per day before starting treatment with buprenorphine. This is because buprenorphine can cause withdrawal symptoms in patients who are dependent on methadone.

During your treatment, your doctor may increase your dose of buprenorphine to a maximum single daily dose of 32 mg, depending upon how you get on. After a period of successful treatment, your doctor may gradually reduce your dose. With careful medical supervision, your dose may continue to be reduced until it is stopped altogether.

Your doctor may wish to perform some tests to assess how well your liver is working before starting treatment with Buprenorphine Sublingual Tablets, and at regular intervals during treatment.

Buprenorphine Sublingual Tablets must not be used by children or adolescents under 16 years old.

If you take more Buprenorphine Sublingual Tablets than you should
Tell your doctor immediately or contact your nearest hospital casualty department. Remember to take the pack and any remaining tablets with you.

If you forget to take Buprenorphine Sublingual Tablets
You should tell your doctor and follow their instructions. Do not take a double dose to make up for the missed dose, unless your doctor tells you to.

If you stop taking Buprenorphine Sublingual Tablets
Do not suddenly stop taking the tablets unless told to do so by your doctor, as this may cause withdrawal symptoms.

4. Possible side effects

Like all medicines, Buprenorphine Sublingual Tablets can cause side effects, although not everyone gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms after taking these tablets, you should contact your doctor immediately:

- Any sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat
- Feeling and blurring of the skin, mouth, eyes and genitals
- Rash affecting your whole body.

If you develop severe fatigue, loss of appetite or if your skin or eyes look yellow, tell your doctor immediately.

The following side effects have also been reported:

The most common side effects are:
- Constipation, headache, difficulty in sleeping, weakness or lack of energy.
- Drowsiness, nausea and vomiting (feeling and being sick), fainting and dizziness (especially when changing position from sitting or lying down to standing) and sweating.
Module 4
Labelling

BUPRENORPHINE 2MG Sublingual Tablets
Buprenorphine
Morningside Healthcare Ltd.

Each sublingual tablet contains 2mg of buprenorphine (as buprenorphine hydrochloride), also contains lactose. Refer to leaflet for further information.

For sublingual use: To be dissolved under the tongue. Do not swallow or chew. Refer to package leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Do not store above 30°C.
Store in original package to protect from moisture.

Manufacturing Authorisation Holder: Morningside Healthcare Ltd.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Buprenorphine 2mg and 8mg Tablets (PL 20117/0119-20; UK/H/1827/002-3/DC) could be approved. The products are prescription-only medicines for opioid drug dependence, within a framework of medical, social and psychological treatment.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83 EC, as amended, claiming to be generic medicinal products of Subutex 2mg and 8mg Sublingual Tablets, which were originally granted to Reckitt and Colman in the UK on 24th April 1995 and have been with the current marketing authorisation holder (Schering Plough) since 22nd December 1998.

The active ingredient, buprenorphine hydrochloride, is an opioid partial agonist/antagonist that 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 that, over a prolonged period, minimises the need of the addicted patient for drugs.

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 studies were 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 and assembly of this product. The manufacturing site is within the Community and the RMS has accepted a copy of the current manufacturer authorisation issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at that site.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Buprenorphine 2mg Sublingual Tablets  
Buprenorphine 8mg Sublingual Tablets |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Buprenorphine hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Drugs used in opioid dependence (N07B C01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>2mg and 8mg sublingual tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1827/002-3/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20117/0119-20</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Morningside Healthcare Limited, 115 Narborough Road, Leicester LE3 0PA, United Kingdom</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS
S.  Active substance
INN/Ph.Eur name:  Buprenorphine hydrochloride

Chemical name:  \((2S)-2-[17-(\text{cyclopropylmethyl})-4,5\alpha\text{-epoxy-3-hydroxy-6-methoxy-6\alpha,14-ethano-14\alpha-morphinan-7\alpha-yl}]-3,3\text{-dimethylbutan-2-ol hydrochloride}\)

Structural formula:

\[ \text{HO} \quad \text{N} \quad \text{HCl} \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{C(\text{CH}_3)_3} \]

Molecular formula:  \(\text{C}_{29}\text{H}_{42}\text{ClNO}_4\)

Appearance:  A white or almost white, crystalline powder

Solubility:  Sparingly soluble in water, freely soluble in methanol, soluble in alcohol, practically insoluble in cyclohexane.

Molecular weight:  504.1

Chirality:  The molecule has seven chiral centres

Buprenorphine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Pharmacopoeia monograph.

P.  Medicinal Product
Other ingredients
Other ingredients consist of pharmaceutical excipients lactose monohydrate, mannitol (E421), maize starch, citric acid anhydrous, sodium citrate, povidone (Pasdone K29/32), magnesium stearate, ascorbic acid, edetic acid (EDTA).

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with the respective monograph.
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from milk from healthy animals, collected under the same conditions as milk for human consumption, and is prepared with calf rennet. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the development programme was to formulate stable, efficacious and tolerable film-coated tablets containing buprenorphine hydrochloride that can be considered generic medicinal products of Subutex 2mg and 8mg Sublingual Tablets (Schering Plough Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The finished product specifications proposed for both strengths are acceptable. 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.

**Container-Closure System**
Both strengths of tablets are packaged in white opaque polyvinylchloride/polyvinylidene chloride/aluminium blisters contained in cardboard boxes. Pack sizes for both strengths are 7, 14 and 28 tablets. Not all pack sizes are to be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

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.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with the storage conditions ‘Store in the original package to protect from moisture’ and ‘Do not store above 30°C’.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies and to place the first three commercial-scale batches of each strength on stability.
Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been 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, as amended. 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.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
Pharmacodynamic, pharmacokinetic and toxicological properties of buprenorphine hydrochloride are well-known. As buprenorphine hydrochloride is a widely used, well-known active substance, no further studies are required and the applicant has provided none. The applicant’s non-clinical overview is satisfactory, providing an appropriate review of the drug’s pharmacology and toxicology.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Buprenorphine 8mg Sublingual Tablets versus the reference product Subutex 8mg Sublingual Tablets (Schering Plough Limited, Belgium) in healthy male volunteers under fasted conditions.

Volunteers were dosed with either treatment. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 144 hours post dose. The two treatment arms were separated by a 5-day washout period. Oral ondansetron 8mg tablets were also permitted as an anti-emetic, if required.
The results are presented below:

### Buprenorphine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Buprenorphine</th>
<th>Subutex</th>
<th>Ratio T/R %</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>5.92</td>
<td>5.69</td>
<td>104.04</td>
<td>90-118</td>
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<tr>
<td>$AUC_{0-t}$</td>
<td>38.65</td>
<td>37.46</td>
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<td>92-119</td>
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<tr>
<td>$AUC_{0-inf}$</td>
<td>40.88</td>
<td>39.36</td>
<td>103.86</td>
<td>93-120</td>
</tr>
</tbody>
</table>

### Nor-Buprenorphine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Buprenorphine</th>
<th>Subutex</th>
<th>Ratio T/R %</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>1.09</td>
<td>1.31</td>
<td>70-106</td>
<td>97.99</td>
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<tr>
<td>$AUC_{0-t}$</td>
<td>25.15</td>
<td>25.54</td>
<td>104.04</td>
<td>74-170</td>
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<tr>
<td>$AUC_{0-inf}$</td>
<td>32.11</td>
<td>31.99</td>
<td>100.37</td>
<td>71-172</td>
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</tbody>
</table>

The test and reference products are within conventional 90% CI limits of 80-125% for buprenorphine, but not for nor-buprenorphine. As this metabolite only displays 1/50th of the activity of the parent drug, it cannot be considered to add significantly to its activity. Therefore, the results for the metabolite are not required to be measured and can be disregarded for the purposes of demonstrating bioequivalence.

In conclusion, bioequivalence has been shown between the test and reference products. As these products meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 8mg strength can be extrapolated to the 2mg strength tablets.

### Efficacy

No new data on the efficacy of buprenorphine hydrochloride are submitted and none are required for these types of applications.

### Safety

During the bioequivalence study, a total of 160 adverse events were reported. Of these, 78 were associated with Subutex and 82 with the test formulation. There were no serious adverse events.

No new safety concerns were raised by the bioequivalence data.

### SPC, PIL, Labels

The SPC, PIL and labels are medically acceptable. The SPCs are consistent with that for the originator products.

### Conclusion

The grant of marketing authorisations is recommended.
IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Buprenorphine 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 risk-benefit balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Buprenorphine 8mg Sublingual Tablets and the originator product Subutex 8mg Sublingual Tablets (Schering Plough Limited). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 8mg strength can be extrapolated to the 2mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for Subutex 8mg Sublingual Tablets (Schering Plough Limited).

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with buprenorphine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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