



Public Assessment Report

Decentralised Procedure

Tephine 200 microgram and 400 microgram Sublingual Tablets
Buprenorphine 200 microgram and 400 microgram Sublingual Tablets

UK/H/1943/001-2/DC

UK/H/1944/001-2/DC

UK/H/1945/001-2/DC

UK licence numbers: PL 04416/0956-957, 0958-959 & 1169-70

Sandoz Limited

LAY SUMMARY

On 2nd September 2011, the MHRA granted Sandoz Limited Marketing Authorisations (licences) for the medicinal products Buprenorphine 200 microgram and 400 microgram Sublingual Tablets. The products are licensed under the following trade names but will be referred to by the generic names, Buprenorphine 200 microgram and 400 microgram Sublingual Tablets, in the remainder of this report:

PL 04416/0956-57 – Tephine 200 microgram and 400 microgram Sublingual Tablets

PL 04416/0958-59 – Buprenorphine 200 microgram and 400 microgram Sublingual Tablets

PL 04416/1169-70 – Buprenorphine 200 microgram and 400 microgram Sublingual Tablets

These are prescription-only medicines (POM). The active ingredient, buprenorphine, is a strong painkiller that belongs to a group of medicines called opioids. It is used to treat severe pain, such as pain following surgery or injury, in heart attacks and in cancer. Buprenorphine is not used to treat headache, toothache, migraine or other pains treatable with weaker painkillers and/or medicines that relieve spasms.

Buprenorphine 200 microgram and 400 microgram Sublingual Tablets were considered to be generic versions of the UK reference products, Temgesic 200 microgram and 400 microgram Sublingual Tablets (PL 36699/0004-5, RB Pharmaceuticals Limited), based on the data submitted by Sandoz Limited.

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Buprenorphine 200 microgram and 400 microgram Sublingual Tablets outweigh the risk; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	UK/H/1943/001-2/DC - PL 04416/0956-57 - Tephine 200 microgram and 400 microgram Sublingual Tablets UK/H/1944/001-2/DC - PL 04416/0958-59 - Buprenorphine 200 microgram and 400 microgram Sublingual Tablets UK/H/1945/001-2/DC - PL 04416/1169-70 - Buprenorphine 200 microgram and 400 microgram Sublingual Tablets
Type of Application	Generic, Article 10(1)
Active Substance	Buprenorphine
Form	Sublingual tablets
Strength	200 microgram and 400 microgram
MA Holder	Sandoz Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom
Reference Member State (RMS)	UK
Concerned Member States (CMS)	UK/H/1943/001-2/DC: Denmark and Germany UK/H/1944/001-2/DC: Germany UK/H/1945/001-2/DC: Germany
Procedure Numbers	UK/H/1943/001-2/DC UK/H/1944/001-2/DC UK/H/1945/001-2/DC
Timetable	End of Procedure: Day 210 – 6 th July 2011

Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Tephine 200 microgram and 400 microgram Sublingual Tablets (PL 04416/0956-57), Buprenorphine 200 microgram and 400 microgram Sublingual Tablets (PL 04416/0958-59) and Buprenorphine 200 microgram and 400 microgram Sublingual Tablets (PL 04416/1169-70) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Tephine 200 microgram Sublingual Tablets
 Tephine 400 microgram Sublingual Tablets
 Buprenorphine 200 microgram Sublingual Tablets
 Buprenorphine 400 microgram Sublingual Tablets
 Buprenorphine 200 microgram Sublingual Tablets
 Buprenorphine 400 microgram Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200/400 microgram of buprenorphine (as buprenorphine hydrochloride).
 Excipient: 45.0/44.8 mg lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet.

For 200 mcg: White, round tablet.
 For 400 mcg: White, oval tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tephine/Buprenorphine is used as a strong analgesic for the relief of severe pain, e.g. following surgery or injuries, myocardial infarction and in cancer.

Use of Tephine/Buprenorphine is NOT indicated in the treatment of headache, toothache, migraine or other conditions involving pain which can be treated using peripherally active analgesics and/or spasmolytics.

4.2 Posology and method of administration

Dosage

The dosage of Tephine/Buprenorphine should generally be adjusted to the intensity of the pain and the individual sensitivity of the patient.

For 200 mcg: The recommended single dose in patients with a bodyweight greater than 45 kg is 1 – 2 sublingual tablets Tephine/Buprenorphine 200 microgram

For 400 mcg: The recommended single dose in patients with a bodyweight greater than 45 kg is 1 sublingual tablet Tephine/Buprenorphine 400 microgram

The onset of effects generally occurs within 30 minutes after sublingual administration.
 The average duration of effects is 6 – 8 hours.

For 200 mcg: If necessary, 1 – 2 sublingual tablets Tephine/Buprenorphine 200 microgram may be administered every 6 – 8 hours.

For 400 mcg: If necessary, 1 sublingual tablet Tephine/Buprenorphine 400 microgam may be administered every 6 – 8 hours.

In severe chronic pain, the dose of Tephine/Buprenorphine should be adjusted to the intensity of the pain and administered regularly in accordance with a fixed schedule corresponding to the duration of effects.

Patients with a bodyweight of 35 – 45 kg should be given a single dose of 1 sublingual tablet Tephine/Buprenorphine 200 microgam, if necessary, every 6 – 8 hours. This is equivalent to an average single dose of 5 micrograms/kg bodyweight.

Patients with a bodyweight of 16 – 35 kg should be given a single dose of 100 microgam of buprenorphine, if necessary, every 6 – 8 hours. Tephine/Buprenorphine 200 microgam sublingual tablets are not divisible. Other buprenorphine containing products covering the 100 microgam dosage are available.

Buprenorphine should not be used in children less than 2 years of age or in children weighing less than 16 kg.

Patients with hepatic insufficiency:

Buprenorphine is metabolised in the liver. The degree and duration of its effects in patients with impaired hepatic function may therefore be altered. It is thus advisable to appropriately adjust the dose of Tephine/Buprenorphine in this patient group.

Method of administration

The sublingual tablets are placed under the tongue, where they will dissolve within 5 – 10 minutes. In the presence of very dry oral mucosa, a few drops of liquid will accelerate the dissolution process.

The sublingual tablets must not be sucked, chewed or swallowed.

At the beginning of treatment, ambulatory patients should rest during and for 1 – 2 hours after administration of Tephine/Buprenorphine.

Duration of use

Tephine/Buprenorphine should not be used for longer than is absolutely necessary. If longer term pain management is required, it is advisable to reassess at regular and frequent intervals (with administration pauses, if applicable) whether and at what dosage Tephine/Buprenorphine should continue to be administered.

There is currently insufficient clinical experience of longer term use of buprenorphine in children.

4.3 Contraindications

Hypersensitivity to buprenorphine, centrally active analgesics or to any of the excipients of the medicinal product (see section 6.1)

Opioid-dependent patients and for drug-substitution treatment

Severe respiratory insufficiency

Severe hepatic insufficiency

Patients treated concurrently with MAO inhibitors or who have used these in the previous 2 weeks (see section 4.5)

4.4 Special warnings and precautions for use

Buprenorphine should be used only under close monitoring and with particular caution:

- in case of impaired respiratory function (e.g. in acute asthma, obstructive pulmonary disorders, cor pulmonale, hypoxia, hypercapnia or pre-existing respiratory depression)
- in patients with head injuries, cerebral damage or pre-existing elevated intracranial pressure. In common with other potent analgesics, buprenorphine can cause elevation of cerebrospinal pressure. In combination with the depressant effect on respiration, this effect can be significantly increased in the presence of head injuries. As buprenorphine can also cause miosis and influence the degree of consciousness, the clinical course of patients with head injuries may be masked and the evaluation of their condition more difficult.

Buprenorphine should be used only with particular caution:

- in elderly and debilitated patients
- in the presence of impaired renal function or renal insufficiency (e.g. Addison's disease)
- in patients with myxoedema or hypothyroidism
- in toxic psychosis, central nervous depression or coma
- in acute alcoholism or delirium tremens
- in kyphoscoliosis with restrictive disturbances of the airways
- in patients who have recently been treated with narcoanalgesics.

It has been demonstrated in controlled studies in humans and animals that buprenorphine has a lower dependency potential than pure opioid agonists. Minor euphoric effects of buprenorphine have been observed in humans. This could result in abuse of the substance to some extent. Caution should therefore be exercised if buprenorphine is prescribed for patients with a known or suspected history of drug abuse.

In addition, buprenorphine should be used with particular caution and at a reduced dose in prostatic hypertrophy, constriction of the urinary tract and biliary tract disorders.

As is the case with all opioids, chronic use of buprenorphine can result in development of physical dependence. Withdrawal symptoms (abstinence syndrome) – should they occur at all – tend to be mild, commence after 2 days and may persist for up to 2 weeks. Withdrawal symptoms include excitation, anxiety states, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal complaints.

Use of Tephine/Buprenorphine can lead to positive results in doping tests. Abuse of the medicinal product Tephine/Buprenorphine for doping purposes can endanger health.

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.

Diversion of buprenorphine has been reported. 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 risks of overdose, spread of blood borne viral infections and respiratory depression.

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).

A reduction of hepatic perfusion induced when certain general anaesthetics, such as halothane, and other medicinal products are used may reduce the rate of hepatic elimination of buprenorphine.

Buprenorphine should be used cautiously together with:

- Benzodiazepines: This combination may potentiate respiratory depression of central origin, with risk of death.
- 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 (see section 4.3).
- CYP3A4 inhibitors and inducers: in a study of the interactions of buprenorphine with ketoconazole, elevated concentrations of buprenorphine and norbuprenorphine were measured. Patients treated with CYP3A4 inhibitors (e.g. ketoconazole, gestodene, triacetyleandomycin, the HIV protease inhibitors ritronavir, indinavir, saquinavir and atazanavir) should therefore be closely monitored and may require a lower dose of buprenorphine.

The interaction of buprenorphine with CYP3A4 inducers has not been investigated to date. It is therefore recommended that patients treated with CYP3A4 inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) be closely monitored if buprenorphine is administered concomitantly.

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

To date, no notable interaction has been observed with cocaine, the agent most frequently used by multi-drug abusers in association with opioids.

4.6 Fertility, pregnancy and lactation

There are insufficient data on the use of buprenorphine during pregnancy and the lactation period. Animal studies have demonstrated reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

The administration of high doses of buprenorphine towards the end of pregnancy, even if only over the short term, may induce respiratory depression in the neonate. Chronic use of buprenorphine during the final trimester of pregnancy may be responsible for withdrawal symptoms in neonates. **Tephine/Buprenorphine** is not recommended for use during pregnancy.

Buprenorphine may be used during pregnancy only if this appears to be absolutely necessary after careful weighing of the potential risks against the expected benefits. In this case, close monitoring of the pregnant women, the foetus and the neonate by the physician are essential.

Buprenorphine and its metabolites are excreted in human milk. In rats buprenorphine has been found to inhibit lactation. Therefore, breast-feeding should be discontinued during treatment with **Tephine/Buprenorphine**.

4.7 Effects on ability to drive and use machines

Even when used as recommended, buprenorphine can influence reactions to such an extent that, for example, driving or operating machines is not recommended during treatment with buprenorphine.

This is particularly the case if there is concurrent use of centrally active substances, including alcohol, tranquillizers, sedatives and hypnotics. The treating physician should provide recommendations in each individual case.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequency conventions:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $<1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

The most commonly reported undesirable effect of buprenorphine is tiredness. Sleep, from which the patient can be easily wakened, occurs most frequently during use in the postoperative phase.

Table 1. Undesirable effects associated with the treatment:

General disorders and administration site conditions	
Common:	flushing
Immune system disorders	
Uncommon:	Generalised (systemic) hypersensitivity reactions
Very rare:	Anaphylactic shock
Psychiatric disorders	
Uncommon:	Confusion, disorientation, nervousness, depression, psychosis, hallucinations, depersonalisation, euphoria, dysphoria, agitation (restlessness)
Nervous system disorders	
Very common:	Tiredness, sleep disturbances, drowsiness
Common:	Dizziness, headache
Uncommon:	Exhaustion, dry mouth, slurred speech, coma, tremor (shaking), seizures, lack of muscle coordination

Eye disorders	
Common:	Miosis
Uncommon:	Double vision, visual disturbances, conjunctivitis
Ear and labyrinth disorders	
Uncommon:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia, bradycardia, cyanosis, AV block
Vascular disorders	
Common:	Orthostatic hypotension
Uncommon:	Hypertension
Respiratory, thoracic and mediastinal disorders	
Common:	Respiratory depression
Uncommon:	Dyspnoea (respiratory distress), apnoea (respiratory arrest)
Very rare:	Bronchospasm
Gastrointestinal disorders	
Common:	Nausea, vomiting
Uncommon:	Constipation, dyspepsia, loss of appetite, diarrhoea
Skin and subcutaneous tissue disorders	
Common:	Sweating
Uncommon:	Paraesthesia, pruritus (itching), skin rash, pallor, urticaria
Very rare:	Angioneurotic oedema (Quincke's oedema)
Renal and urinary disorders	
Uncommon:	Micturition disorders, urinary retention

The following undesirable effects have also been reported during use of buprenorphine in drug-substitution treatment: **Nervous system:** insomnia, sleepiness, **Cardiovascular system:** fainting, fall in blood pressure, **Respiratory tract:** respiratory depression, **Liver:** hepatic necrosis and hepatitis.

Circulatory dysregulation may occur on initial use of buprenorphine.

Local irritation of the oral mucosa (in some cases with development of mouth ulcers and haemorrhagic diathesis) can occur after use of buprenorphine.

In opioid-dependent patients, first administration of buprenorphine may induce withdrawal symptoms comparable to those seen after use of naloxone.

The safety profile of buprenorphine in children is comparable with that in adults.

4.9 Overdose

Even doses in the therapeutic range may cause serious poisoning (intoxications) in subjects who are hypersensitive (particularly children). The symptoms of excessive effects of buprenorphine are characterised by signs such as “feeling strange”, poor ability to concentrate, sleepiness and (possibly) a sensation of dizziness when standing. Other symptoms of overdose are respiratory depression, (reduced respiratory rate and/or respiratory volume, Cheyne-Stokes respiration, cyanosis), extreme sleepiness, disturbance of consciousness with coma in extreme cases, miosis, flaccidity of the skeletal muscles, moist-cold skin, bradycardia and hypotension.

Massive intoxication can induce respiratory arrest, circulatory failure, cardiac arrest and result in death.

Treatment:

In case of overdose, the cardiac and respiratory status of the patient must be closely monitored and appropriate supportive measures should be initiated. A specific opioid antagonist, such as naloxone, can counteract the effects of buprenorphine. Higher doses are generally required for this purpose than with other opioids. It must be borne in mind that the duration of effects of opioids can exceed that of naloxone, so that there is a risk of recurrence of respiratory depression.

Gastric lavage should be considered if larger doses of **Tephine/Buprenorphine** have been ingested.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Potent analgesic, partial opioid receptor agonist
ATC code: N02A E01

Buprenorphine is a potent, centrally active analgesic with opioid-agonistic and opioid-antagonistic properties. The analgesic effect is attributable to interaction with specific opioid receptors (mainly μ -receptors) in the central nervous system. The long duration of effects (6 – 8 hours) is attributed to the slow rate of dissociation of buprenorphine from receptors and the limited extent to which the effects are counteracted by morphine antagonists because of the high affinity of buprenorphine for the receptor.

Buprenorphine can induce a fall (or rarely, also an increase) in heart rate and blood pressure and also has antitussive and respiratory depressive effects.

If buprenorphine is administered after pure opioid agonists, its antagonistic effects may be manifested dependent on the dose administered, i.e. the effects of the agonists, such as morphine, may be attenuated or abolished.

5.2 Pharmacokinetic properties

Absorption

The absorption of buprenorphine after sublingual administration is good. The onset of analgesic effects commences approximately 30 minutes after sublingual administration. The effects peak after 60 – 120 minutes and persist for 6 – 8 hours.

Peak plasma concentrations are reached within approximately 200 minutes after sublingual administration. Following intravenous injection of buprenorphine, plasma concentrations fall rapidly in the initial phase with a half-life of 2 – 5 minutes (distribution phase). Terminal half-life is approximately 3 hours. The concentrations of the active substance 10 minutes after i.m. injection are equivalent to those after i.v. injection. Terminal half-life after i.m. administration is also 3 hours. Because of the persistent receptor binding, pharmacodynamic effects do not correlate with blood concentrations or the elimination half-life of buprenorphine.

In human plasma, 96% of a buprenorphine dose is bound to plasma proteins, mainly to α - and β -globulins. An influence on the protein binding of anticoagulants (bound to albumin) is therefore unlikely.

Metabolism and elimination

Buprenorphine is metabolised in the liver. It is subject to a phase 1 (N-dealkylation) and a phase 2 (O- and/or N-glucuronidation) metabolism.

Unchanged buprenorphine and its metabolites are also excreted by the biliary route.

Elimination occurs within 7 days, mainly via the faeces but 27% of a dose is eliminated in the urine.

While predominantly unchanged buprenorphine has been detected in faeces, glucuronide derivatives of buprenorphine and N-dealkylbuprenorphine are mainly found in the urine. The slow rate of faecal excretion indicates the presence of an enterohepatic circulation.

Passage into cerebrospinal fluid

Buprenorphine crosses the blood-brain barrier and is detectable in all sections of the brain. The concentration is highest in the pituitary gland and lower in the cerebellum and spinal marrow.

Placental passage

Studies conducted in gestating rats have shown that buprenorphine crosses the placental barrier. The concentrations of buprenorphine in foetal tissue in the early phase of pregnancy are equivalent to maternal plasma levels. With progression of the pregnancy, buprenorphine can also be detected in the gastrointestinal tract of the foetus in some cases.

Only immediately prior to birth is the foetal liver capable of metabolising buprenorphine and the substance is then found in the form of derivatives in the gastrointestinal tract of the foetus.

Passage into breast milk

Studies conducted in rats have demonstrated that buprenorphine passes into breast milk.

5.3 Preclinical safety data

No undesirable effects on fertility or general reproductive potential have been observed in rats. However, evidence of fetotoxic effects and an increased rate of postimplantation losses have been reported from studies in the rat and rabbit.

Studies in rats have demonstrated a reduced rate of intrauterine growth, delayed development of certain neurological functions and a high rate of peri- and postnatal mortality of offspring after treatment of the maternal animals during the gestation/lactation period. There is evidence that problems relating to parturition and reduced milk production contributed to these effects. There were no signs of embryotoxic or teratogenic effects in the rat or rabbit.

No clinically relevant effects are reported from in vitro and in vivo studies of the mutagenic potential of buprenorphine.

No evidence of a carcinogenic potential relevant to humans has been identified in long-term studies in the rat and mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous
Lactose monohydrate
Mannitol
Sodium citrate
Sodium stearyl fumarate
Pregelatinised starch (maize)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister packs

Pack sizes 7, 10, 20, 24, 28, 30, 48, 50 or 70 sublingual tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0956
PL 04416/0957
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PL 04416/1169
PL 04416/1170

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/09/2011

10 DATE OF REVISION OF THE TEXT

02/09/2011

Module 3

Patient Information Leaflet

Tephine 200 microgam and 400 microgam Sublingual Tablets – PL 04416/0956-7

PACKAGE LEAFLET: INFORMATION FOR THE USER

SZ00000LT000

Tephine 200 microgam Sublingual Tablets Tephine 400 microgam 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 Tephine is and what it is used for
2. Before you take Tephine
3. How to take Tephine
4. Possible side effects
5. How to store Tephine
6. Further information



1 What Tephine is and what it is used for

Tephine is a **strong painkiller** that belongs to a group of medicines called opioids.

It is used to treat:

- **severe pain**, such as pain following surgery or injury, in heart attacks and in cancer

Tephine is not used to treat headache, toothache, migraine or other pains treatable with weaker painkillers and/or medicines that relieve spasms.

2 Before you take Tephine

Do not take Tephine if you are/have

- **allergic** (hypersensitive) to:
 - buprenorphine or other painkillers acting in the brain or spinal cord
 - any of the other ingredients of this medicine
 - **dependent on opioids** or for withdrawal treatment from opioids
 - serious **breathing problems**
 - a serious **liver disease**
 - treated or have been treated in the previous 2 weeks with medicines known as monoamine oxidase inhibitors, such as moclobemide
- These types of **medicines** are used to **treat depression or Parkinson's disease**.

Using other medicines

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

The following medicines can affect or be affected by Tephine:

- **medicines that reduce the blood flow** through the liver, such as halothane
- **medicines which calm, induce sleep or relax muscles** with active substance names ending with "azepam", such as diazepam, temazepam
Do not take these medicines while taking Tephine, unless your doctor says it is absolutely necessary. This combination can be fatal if the correct dose is not carefully determined.
- **medicines to treat epilepsy or to sedate**, with active substance names mostly ending with "tal", such as phenobarbital
- other **medicines used to treat anxiety or sleep disorders**
- other **strong painkillers** or medicines to treat cough, such as codeine, dihydrocodeine, morphine
- certain medicines to treat depression or Parkinson's disease known as **monoamine oxidase inhibitors**, such as moclobemide
Do not take Tephine while taking these medicines.
- **medicines to treat allergies**, sleep disturbances or cold; or prevent and treat nausea and vomiting; such as doxylamine, diphenhydramine.
- **medicines to treat mental or anxiety disorders**, with sedative effects, such as chlorpromazine, haloperidol
- certain medicines to treat high blood pressure, such as **clonidine**
- Your doctor may prescribe you a lower Tephine dose if you take any of the following medicines:

Take special care with Tephine

Inform your doctor if any of the following apply to you:

- reduced breathing function such as:
 - acute asthma
 - disorders with narrowed lung airways
 - enlarged right heart chamber due to continuing overload of the blood circulation through the lung
 - reduced oxygen supply
 - increased levels of carbon dioxide in the blood
 - shallow breathing

Your doctor will only prescribe you Tephine under his/her close supervision if any of these breathing difficulties apply to you. You must not use Tephine if you have serious breathing problems.

- in the case of head or brain injuries or increased pressure inside the skull
Your doctor will only prescribe you Tephine under his/her close supervision if any of these cases apply to you.
- a history of medicine abuse or emotional instability
- disorder of the tube-like structures that carry bile
- reduced kidney function
- reduced function of the cortex of the two glands situated above the kidneys
- underactive thyroid or accumulation of mucus and fluid in the fat tissues with swelling known as myxoedema
- psychosis due to medicines
- central nervous depression or coma
- enlarged prostate or narrowing of the urethra
- acute alcoholism or alcohol delirium
- deformity of the spinal column
- have been treated recently with narcotic pain killers

Patients weighing less than 35 kg

Tephine 200 microgram and 400 microgram are not recommended for these patients.

Patients weighing less than 45 kg

Tephine 400 microgram is not recommended for these patients.

Elderly and weak patients

Tephine should only be used in these patients with particular caution.

Effects of misuse for doping

Using of Tephine can lead to positive results in doping tests. Abusing Tephine for doping purposes can endanger your health.

- **ketoconazole**: a medicine to treat fungal infections
- medicines to treat HIV infections, such as ritonavir, saquinavir, indinavir, atazanavir
- oral contraceptive medicines containing **gestodene**
- **medicines to treat infections** with active substance names ending in "mycin", such as erythromycin
- Your doctor may prescribe you a higher Tephine dose if you take any of the following medicines:
 - **medicines to treat epilepsy**, such as phenobarbital, carbamazepine, phenytoin
 - **rifampicin**: a medicine to treat bacterial infections
- **phenprocoumon**: a medicine to prevent normal blood coagulation
It is essential that you inform your doctor if you take this medicine. Your doctor will monitor you very closely during Tephine use and may need to adjust the Tephine dose.

Taking Tephine with food and drink

Avoid drinking alcohol or taking any medicines that contain alcohol while taking Tephine.

Pregnancy and breast-feeding

- **Pregnancy**
Tephine is not recommended during pregnancy. Tell your doctor before taking Tephine if you are pregnant, trying or become pregnant during treatment.
- **Breast-feeding**
Discontinue breast-feeding while taking Tephine as it will pass into your milk and may harm the breast-fed child.

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

Driving and using machines

Do not drive or use machines if you feel drowsy while being treated with this medicine.

Tephine can impair alertness and the ability to react.

Therefore, ask your doctor whether and under what circumstances you can drive a vehicle, for example.

Important information about some of the ingredients of Tephine

This medicine 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.

Continued on the next page >>

3 How to take Tephine

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

The usual dose is:

- **Patients weighing more than 45 kg**

- Tephine 200 microgram
- 1-2 tablets as single dose
- If necessary, 1-2 further tablets can be taken every 6-8 hours.

Tephine 400 microgram

- 1 tablet as single dose
- If necessary, 1 further tablets can be taken every 6-8 hours.

- **Patients weighing between 35 and 45 kg**

- Tephine 200 microgram
- 1 tablet as single dose
- If necessary, 1 further tablet can be taken every 6-8 hours.

The dosage interval must be determined by the doctor, based upon observation of the individual patient.

- **Patients with reduced liver function**

Your doctor will probably prescribe a lower dose than those described above. However, you must not use Tephine if you have serious liver diseases.

The Tephine effects onset within 30 minutes following administration and usually last for 6-8 hours. Please talk to your doctor or pharmacist if you feel that the effects are too strong or too weak.

Method of use

The tablets are described as "sublingual". This means that the tablet should be **placed under the tongue** and kept there until fully dissolved. This usually takes 5 to 10 minutes.

In the presence of very dry oral mucosa, a few drops of liquid will accelerate the dissolution process.

Do not suck, chew or swallow the tablets whole – the medicine will not work this way. Do not take the tablets at the same time as food or drink.

Patients who are not confined to bed should rest for 1 to 2 hours after taking Tephine.

Duration of use

This depends on the nature and the severity of the pain and will be decided by the doctor.

- narrowing of the pupils
- low blood pressure
- reduced breathing function
- nausea and vomiting
- sweating

Uncommon, affects 1 to 10 per 1,000 users

- generalized allergic reactions
- confusion, disorientation, nervousness, depression, psychosis, hallucinations, a feeling of loss of personality, euphoria, depression, restlessness, exhaustion
- dry mouth, slurred speech
- coma
- shaking
- seizures
- lack of muscle coordination
- seeing double, visual disturbances
- inflammation causing red, watery and itchy eyes
- ringing in the ears
- high blood pressure
- accelerated or slowed heart rhythm
- bluish discoloration of the skin and particularly of the lips and fingernails as a result of oxygen deficiency in the blood
- disturbed heart conduction
- breathing distress or arrest
- constipation, indigestion, loss of appetite, diarrhoea
- sensory disturbances of the skin
- itching, skin rash, pale skin, hives
- discomfort when emptying the bladder, inability to empty the bladder completely

Very rare, affects fewer than 1 per 10,000 users

- muscle seizures in the lung airways
- swelling of the skin and mucous membranes
- life-threatening allergic shock reaction

Frequency not known, according to the available data

- local irritation of the oral mucosa - in some cases with development of mouth ulcers and a tendency to bleed
- disturbances in the regulation of circulation can occur immediately after use
- in opioid-dependent patients the first administration of Tephine may induce withdrawal symptoms

Other side effects observed in substitution therapy

- sleeplessness
- sleepiness
- fainting
- fall in blood pressure
- liver cell destruction
- liver inflammation

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.

Tephine should only be used for as long as absolutely necessary. Where long-term pain treatment is necessitated, reassessments at frequent, regular intervals, with administration pauses where applicable, are required. These help in deciding if and with which dose Tephine should continue to be administered.

There is currently insufficient experience of long-term Tephine use in children.

If you take more Tephine than you should

Tell your doctor immediately or contact your nearest hospital casualty department. Bring the pack and any remaining tablets with you.

Under all circumstances, you must avoid situations that require increased alertness, such as driving. Somebody must keep the patient awake, give instructions to breathe and provide respiratory assistance until a doctor arrives.

If you forget to take Tephine

Continue with the treatment as recommended. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Tephine

Discuss it with your doctor before interrupting or stopping treatment.

Prolonged Tephine use can result in development of physical dependence. Abrupt discontinuation of the treatment will therefore be associated with withdrawal symptoms. These may include headache, muscle pain, anxiety, states of tension, restlessness, confusion, irritability, recurrent sleeplessness, mood swings, hallucinations and seizures.

The risk of withdrawal symptoms occurring is greater if the treatment is stopped abruptly. Your doctor will gradually reduce the dosage when the treatment is discontinued.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, Tephine can cause side effects, although not everyone gets them.

Side effects can occur with the following frequencies:

Very common, affects more than 1 per 10 users

- drowsiness
- tiredness
- sleep disturbances

Common, affects 1 to 10 per 100 users

- flushes
- dizziness
- headache

5 How to store Tephine

Keep out of the reach and sight of children.

This medicinal product does not require any special storage conditions.

Do not use Tephine after the expiry date, which is stated on the carton and plastic/aluminium strip 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 Tephine contains:

- The **active substance** is **buprenorphine** as buprenorphine hydrochloride.

Tephine 200 microgam Sublingual Tablets

Each tablet contains 200 microgam buprenorphine.

Tephine 400 microgam Sublingual Tablets

Each tablet contains 400 microgam buprenorphine.

- The other ingredients are: citric acid anhydrous, lactose monohydrate, mannitol, sodium citrate, sodium stearyl fumarate, pregelatinised starch (maize).

What Tephine looks like and contents of the pack

Tephine 200 microgam Sublingual Tablets

Tephine 200 microgam Sublingual Tablets are white to off-white, round tablets.

Tephine 400 microgam Sublingual Tablets

Tephine 400 microgam Sublingual Tablets are white to off-white, oval tablets.

Your medicine is available in plastic/aluminium strips containing 7, 10, 20, 24, 28, 30, 48, 50 or 70 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Sandoz Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, UK.

Manufacturer

Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany.

This leaflet was last approved in 07/2011 (to be amended upon approval).

SZ00000LT000

Buprenorphine 200 microgram and 400 microgram Sublingual Tablets PL 04416/0958-9 & 1169-70

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The leaflet texts for PLs 04416/0958-9 and PLs 04416/1169-70 are identical.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Buprenorphine 200 microgram Sublingual Tablets Buprenorphine 400 microgram 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 is and what it is used for
2. Before you take Buprenorphine
3. How to take Buprenorphine
4. Possible side effects
5. How to store Buprenorphine
6. Further information

1. WHAT BUPRENORPHINE IS AND WHAT IT IS USED FOR

Buprenorphine is a **strong painkiller** that belongs to a group of medicines called opioids.

It is used to treat:

- **severe pain**, such as pain following surgery or injury, in heart attacks and in cancer

Buprenorphine is not used to treat headache, toothache, migraine or other pains treatable with weaker painkillers and/or medicines that relieve spasms.

2. BEFORE YOU TAKE BUPRENORPHINE

Do not take Buprenorphine

if you are/have

- **allergic** (hypersensitive) to:
 - buprenorphine or other painkillers acting in the brain or spinal cord
 - any of the other ingredients of this medicine
 - **dependent on opioids** or for withdrawal treatment from opioids
 - **serious breathing problems**
 - a serious **liver disease**
 - treated or have been treated in the previous 2 weeks with medicines known as monoamine oxidase inhibitors, such as moclobemide
- These types of **medicines** are used to **treat depression** or **Parkinson's disease**.

Take special care with Buprenorphine

Inform your doctor if any of the following apply to you:

- reduced breathing function such as:

- acute asthma
- disorders with narrowed lung airways
- enlarged right heart chamber due to continuing overload of the blood circulation through the lung
- reduced oxygen supply
- increased levels of carbon dioxide in the blood
- shallow breathing

Your doctor will only prescribe you Buprenorphine under his/her close supervision if any of these breathing difficulties apply to you. You must not use Buprenorphine if you have serious breathing problems.

- in the case of head or brain injuries or increased pressure inside the skull
Your doctor will only prescribe you Buprenorphine under his/her close supervision if any of these cases apply to you.
- a history of medicine abuse or emotional instability
- disorder of the tube-like structures that carry bile
- reduced kidney function
- reduced function of the cortex of the two glands situated above the kidneys
- underactive thyroid or accumulation of mucus and fluid in the fat tissues with swelling known as myxoedema
- psychosis due to medicines
- central nervous depression or coma
- enlarged prostate or narrowing of the urethra
- acute alcoholism or alcohol delirium
- deformity of the spinal column
- have been treated recently with narcotic pain killers

Patients weighing less than 35 kg

Buprenorphine 200 microgam and 400 microgam are not recommended for these patients.

Patients weighing less than 45 kg

Buprenorphine 400 microgam is not recommended for these patients.

Elderly and weak patients

Buprenorphine should only be used in these patients with particular caution.

Effects of misuse for doping

Using of Buprenorphine can lead to positive results in doping tests. Abusing Buprenorphine for doping purposes can endanger your health.

Using other medicines

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

The following medicines can affect or be affected by Buprenorphine:

- **medicines that reduce the blood flow** through the liver, such as halothane
- **medicines which calm, induce sleep or relax muscles** with active substance names ending with "azepam", such as diazepam, temazepam
Do not take these medicines while taking Buprenorphine, unless your doctor says it is absolutely necessary. This combination can be fatal if the correct dose is not carefully determined.
- **medicines to treat epilepsy or to sedate**, with active substance names mostly ending with "tal", such as phenobarbital
- other **medicines used to treat anxiety or sleep disorders**
- other **strong painkillers** or medicines to treat cough, such as codeine, dihydrocodeine, morphine

- certain medicines to treat depression or Parkinson's disease known as **monoamine oxidase inhibitors**, such as moclobemide
Do not take Buprenorphine while taking these medicines.
- **medicines to treat allergies**, sleep disturbances or cold; or prevent and treat nausea and vomiting; such as doxylamine, diphenhydramine.
- **medicines to treat mental or anxiety disorders**, with sedative effects, such as chlorpromazine, haloperidol
- certain medicines to treat high blood pressure, such as **clonidine**
- Your doctor may prescribe you a lower Buprenorphine dose if you take any of the following medicines:
 - **ketoconazole**: a medicine to treat fungal infections
 - medicines to treat HIV infections, such as ritonavir, saquinavir, indinavir, atazanavir
 - oral contraceptive medicines containing **gestodene**
 - **medicines to treat infections** with active substance names ending in "mycin", such as erythromycin
- Your doctor may prescribe you a higher Buprenorphine dose if you take any of the following medicines:
 - **medicines to treat epilepsy**, such as phenobarbital, carbamazepine, phenytoin
 - **rifampicin**: a medicine to treat bacterial infections
- **phenprocoumon**: a medicine to prevent normal blood coagulation
It is essential that you inform your doctor if you take this medicine. Your doctor will monitor you very closely during Buprenorphine use and may need to adjust the Buprenorphine dose.

Taking Buprenorphine with food and drink

Avoid drinking alcohol or taking any medicines that contain alcohol while taking Buprenorphine.

Pregnancy and breast-feeding

- **Pregnancy**
Buprenorphine is not recommended during pregnancy. Tell your doctor before taking Buprenorphine if you are pregnant, trying or become pregnant during treatment.
- **Breast-feeding**
Discontinue breast-feeding while taking Buprenorphine as it will pass into your milk and may harm the breast-fed child.

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

Driving and using machines

Do not drive or use machines if you feel drowsy while being treated with this medicine.

Buprenorphine can impair alertness and the ability to react. Therefore, ask your doctor whether and under what circumstances you can drive a vehicle, for example.

Important information about some of the ingredients of Buprenorphine

This medicine 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 BUPRENORPHINE

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

The usual dose is:

- **Patients weighing more than 45 kg**
Buprenorphine 200 microgram
- 1 – 2 tablets as single dose
- If necessary, 1 – 2 further tablets can be taken every 6 – 8 hours.

Buprenorphine 400 microgram
- 1 tablet as single dose
- If necessary, 1 further tablets can be taken every 6 – 8 hours.
- **Patients weighing between 35 and 45 kg**
Buprenorphine 200 microgram
- 1 tablet as single dose
- If necessary, 1 further tablet can be taken every 6 – 8 hours.
The dosage interval must be determined by the doctor, based upon observation of the individual patient.
- **Patients with reduced liver function**
Your doctor will probably prescribe a lower dose than those described above. However, you must not use Buprenorphine if you have serious liver diseases.

The Buprenorphine effects onset within 30 minutes following administration and usually last for 6 – 8 hours. Please talk to your doctor or pharmacist if you feel that the effects are too strong or too weak.

Method of use

The tablets are described as “sublingual”. This means that the tablet should be **placed under the tongue** and kept there until fully dissolved. This usually takes 5 to 10 minutes.

In the presence of very dry oral mucosa, a few drops of liquid will accelerate the dissolution process. Do not suck, chew or swallow the tablets whole – the medicine will not work this way. Do not take the tablets at the same time as food or drink.

Patients who are not confined to bed should rest for 1 to 2 hours after taking Buprenorphine.

Duration of use

This depends on the nature and the severity of the pain and will be decided by the doctor.

Buprenorphine should only be used for as long as absolutely necessary. Where long-term pain treatment is necessitated, reassessments at frequent, regular intervals, with administration pauses where applicable, are required. These help in deciding if and with which dose Buprenorphine should continue to be administered.

There is currently insufficient experience of long-term Buprenorphine use in children.

If you take more Buprenorphine than you should

Tell your doctor immediately or contact your nearest hospital casualty department. Bring the pack and any remaining tablets with you.

Under all circumstances, you must avoid situations that require increased alertness, such as driving. Somebody must keep the patient awake, give instructions to breathe and provide respiratory assistance until a doctor arrives.

If you forget to take Buprenorphine

Continue with the treatment as recommended. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Buprenorphine

Discuss it with your doctor before interrupting or stopping treatment.

Prolonged Buprenorphine use can result in development of physical dependence. Abrupt discontinuation of the treatment will therefore be associated with withdrawal symptoms. These may include headache, muscle pain, anxiety, states of tension, restlessness, confusion, irritability, recurrent sleeplessness, mood swings, hallucinations and seizures.

The risk of withdrawal symptoms occurring is greater if the treatment is stopped abruptly. Your doctor will gradually reduce the dosage when the treatment is discontinued.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

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

Side effects can occur with the following frequencies:

Very common, affects more than 1 per 10 users

- drowsiness
- tiredness
- sleep disturbances

Common, affects 1 to 10 per 100 users

- flushes
- dizziness
- headache
- narrowing of the pupils
- low blood pressure
- reduced breathing function
- nausea and vomiting
- sweating

Uncommon, affects 1 to 10 per 1,000 users

- generalized allergic reactions
- confusion, disorientation, nervousness, depression, psychosis, hallucinations, a feeling of loss of personality, euphoria, depression, restlessness, exhaustion
- dry mouth, slurred speech
- coma
- shaking
- seizures
- lack of muscle coordination
- seeing double, visual disturbances
- inflammation causing red, watery and itchy eyes
- ringing in the ears
- high blood pressure
- accelerated or slowed heart rhythm
- bluish discoloration of the skin and particularly of the lips and fingernails as a result of oxygen deficiency in the blood
- disturbed heart conduction
- breathing distress or arrest
- constipation, indigestion, loss of appetite, diarrhoea

- sensory disturbances of the skin
- itching, skin rash, pale skin, hives
- discomfort when emptying the bladder, inability to empty the bladder completely

Very rare, affects fewer than 1 per 10,000 users

- muscle seizures in the lung airways
- swelling of the skin and mucous membranes
- life-threatening allergic shock reaction

Frequency not known, according to the available data

- local irritation of the oral mucosa - in some cases with development of mouth ulcers and a tendency to bleed
- disturbances in the regulation of circulation can occur immediately after use
- in opioid-dependent patients the first administration of Buprenorphine may induce withdrawal symptoms

Other side effects observed in substitution therapy

- sleeplessness
- sleepiness
- fainting
- fall in blood pressure
- liver cell destruction
- liver inflammation

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

Keep out of the reach and sight of children

This medicinal product does not require any special storage conditions.

Do not use Buprenorphine after the expiry date, which is stated on the carton and plastic/aluminium strip 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 contains:

- The active substance is **buprenorphine** as buprenorphine hydrochloride.

Buprenorphine 200 microgram Sublingual Tablets

Each tablet contains 200 microgram buprenorphine.

Buprenorphine 400 microgram Sublingual Tablets

Each tablet contains 400 microgram buprenorphine.

- The other ingredients are: citric acid anhydrous, lactose monohydrate, mannitol, sodium citrate, sodium stearyl fumarate, pregelatinised starch (maize).

What Buprenorphine looks like and contents of the pack

Buprenorphine 200 microgram Sublingual Tablets

Buprenorphine 200 microgram Sublingual Tablets are white to off-white, round tablets.

Buprenorphine 400 microgram Sublingual Tablets

Buprenorphine 400 microgram Sublingual Tablets are white to off-white, oval tablets.

Your medicine is available in plastic/aluminium strips containing 7, 10, 20, 24, 28, 30, 48, 50 or 70 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Sandoz Limited
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.
United Kingdom

Manufacturer

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1, 39179 Barleben
Germany

This leaflet was last approved in

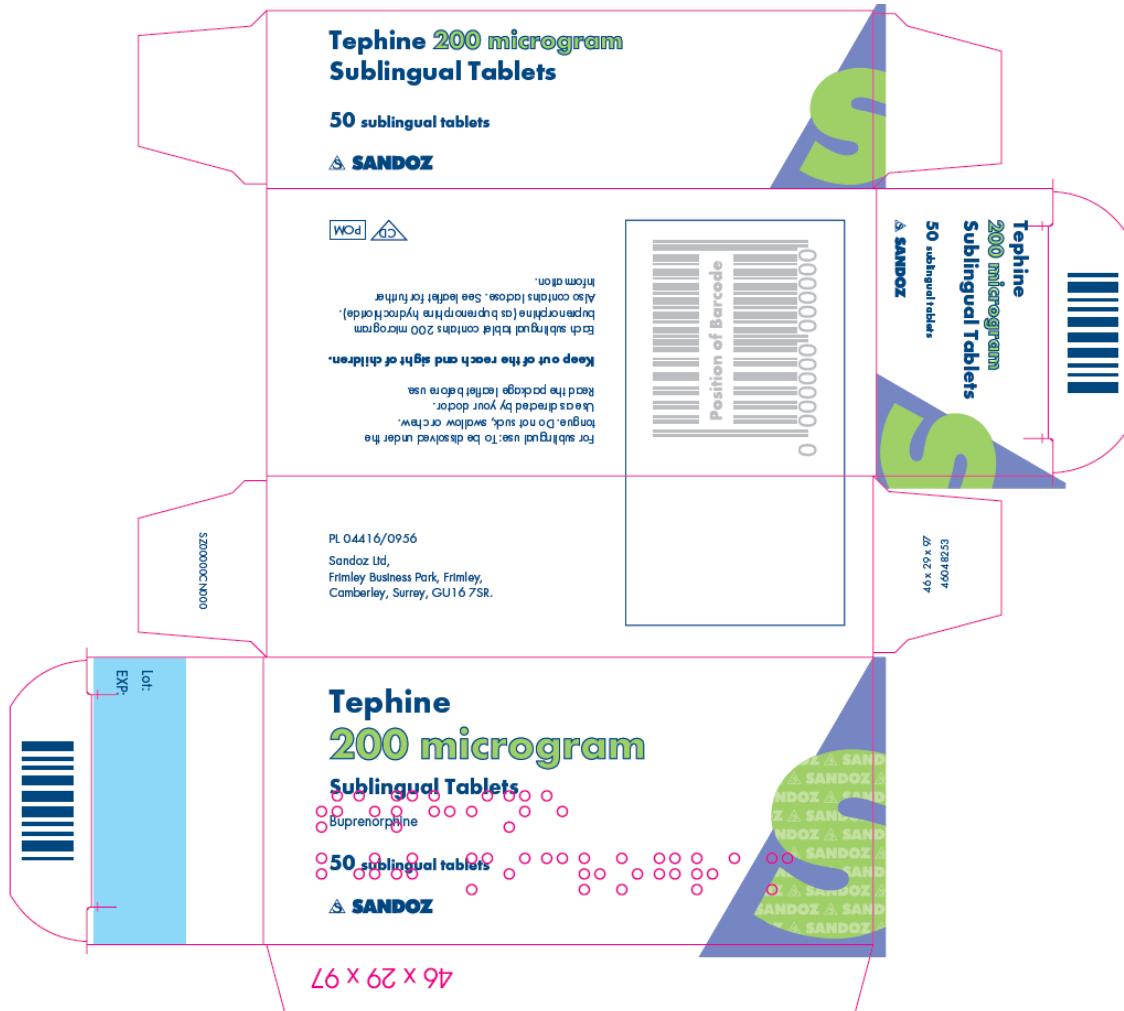
07/07/2011 (to be amended upon approval)

Module 4

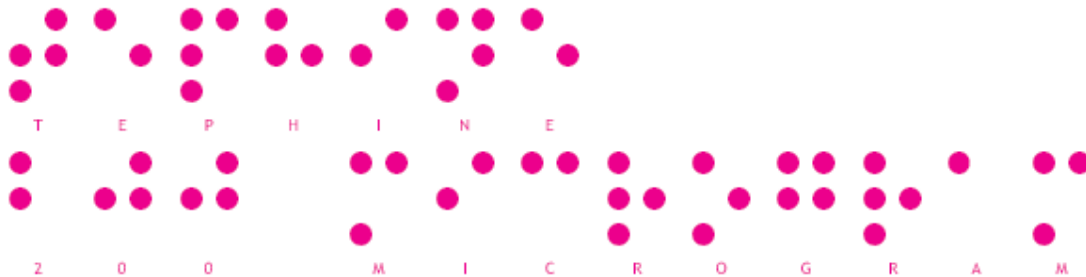
Labelling

Tephine 200 microgram Sublingual Tablets – PL 04416/0956













Carton for blisters, with Braille



Braille translation

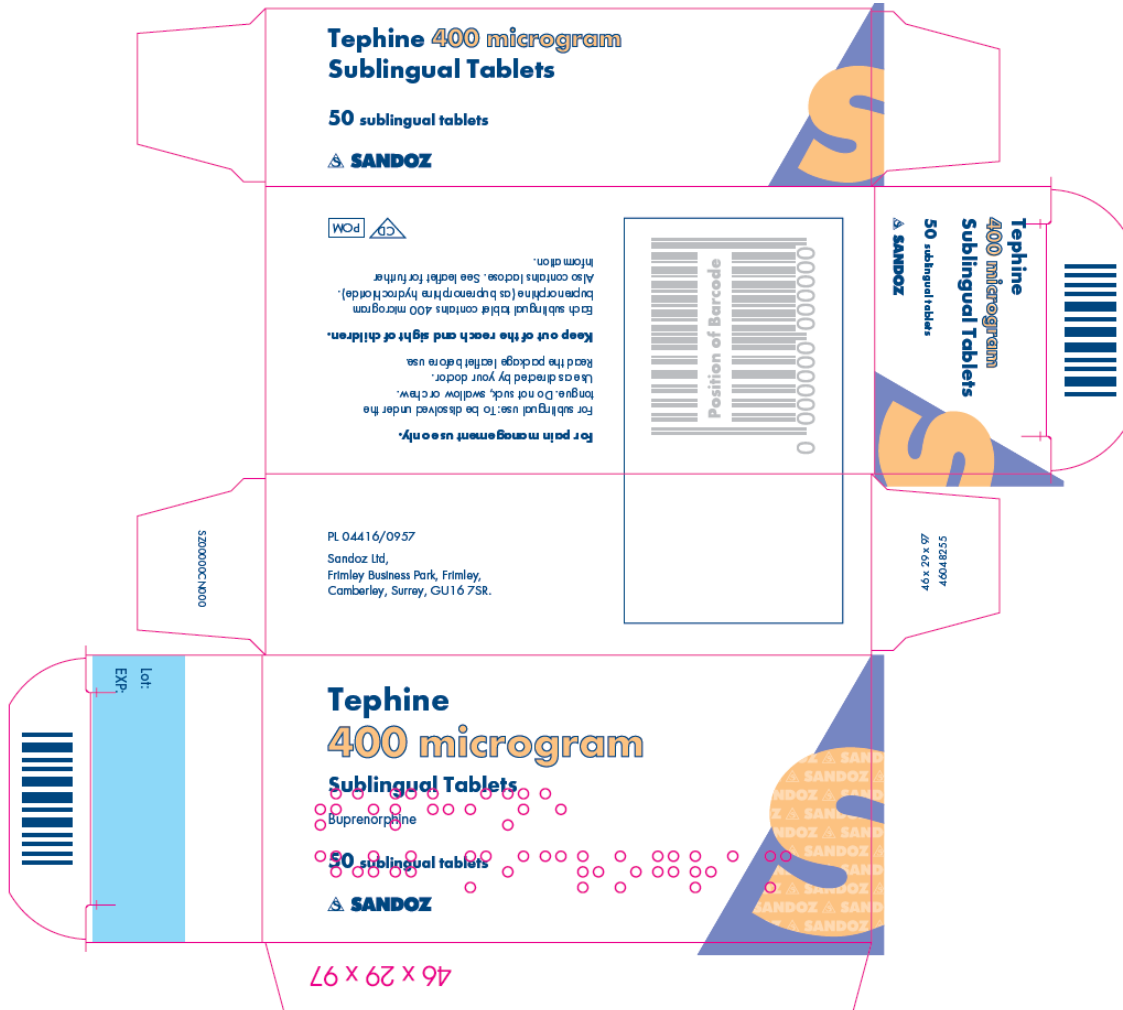


Blister foil

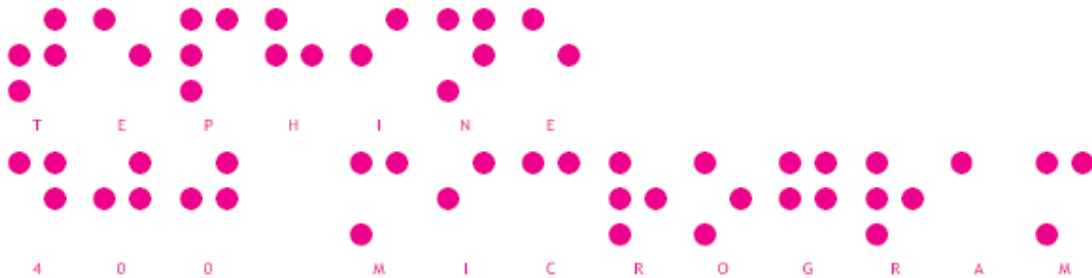
Tephine 200 microgram Sublingual Tablets		Tephine 200 microgram Sublingual Tablets		Tephine 200 microgram Sublingual Tablets	
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Tephine 400 microgram Sublingual Tablets – PL 04416/0957


Carton for blisters, with Braille



Braille translation



Blister foil

Tephine 400 microgram Sublingual Tablets		Tephine 400 microgram Sublingual Tablets		Tephine 400 microgram Sublingual Tablets	
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**Buprenorphine 200 microgram and 400 microgram Sublingual Tablets
PL 04416/0958-9 & 1169-70**

The MAH has submitted a text version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The labelling texts for PLs 04416/0958-9 and PLs 04416/1169-70 are identical apart from the PL numbers.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Buprenorphine 200 microgram Sublingual Tablets
Buprenorphine 400 microgram Sublingual Tablets

Buprenorphine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 200 microgram buprenorphine (as buprenorphine hydrochloride).
Each sublingual tablet contains 400 microgram buprenorphine (as buprenorphine hydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

50 sublingual tablets

Also available in pack sizes of:

7 sublingual tablets
10 sublingual tablets
20 sublingual tablets
24 sublingual tablets
28 sublingual tablets
30 sublingual tablets
48 sublingual tablets
70 sublingual tablets

Not all pack sizes may be marketed, only the quantity will change.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For sublingual use: To be dissolved under the tongue. Do not suck, swallow or chew. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For the 400 microgram:

For Pain Management only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Limited
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR.
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 04416/0958 / PL 04416/1169
PL 04416/0959 / PL 04416/1170

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM
CD

15. INSTRUCTIONS ON USE

Use as directed by your doctor

16. INFORMATION IN BRAILLE

Buprenorphine 200 microgram
Buprenorphine 400 microgram

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PVDC-Aluminium blisters

1. NAME OF THE MEDICINAL PRODUCT

Buprenorphine 200 microgam Sublingual Tablets
Buprenorphine 400 microgam Sublingual Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PL 04416/0958 / PL 04416/1169
PL 04416/0959 / PL 04416/1170

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Sandoz Limited Marketing Authorisations for the medicinal products Tephine 200 microgram and 400 microgram Sublingual Tablets (PL 04416/0956-57; UK/H/1943/001-2/DC) and Buprenorphine 200 microgram and 400 microgram Sublingual Tablets (PL 04416/0958-59 and 119-70; UK/H/1944-5/001-2/DC) on 2nd September 2011. The products are prescription-only medicines.

These are generic applications for Tephine/Buprenorphine 200 microgram and 400 microgram Sublingual Tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The applications refer to the UK products, Temgesic 200 microgram and 400 microgram Sublingual Tablets, originally licensed to Reckitt & Colman (PL 00044/0063 and 0109) on 11th November 1980 and 25th October 1990 respectively. These licences have undergone a series of Change of Ownership (CoA) procedures and were authorised to Schering-Plough Limited (PL 00201/0245 and 0244) on 20th May 1998. These licences underwent a further Change of Ownership (CoA) procedure and were authorised to the current Marketing Authorisation Holder, RB Pharmaceuticals Limited (PL 36699/0004-5) on 29th September 2010. The reference products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired. The European reference product, Temgesic 0.2 mg sublingual tablets, was first authorised to Essex Pharma GmbH in Germany on 22nd December 1982.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Sandoz Limited applied for Marketing Authorisations for Tephine 200 microgram and 400 microgram Sublingual Tablets in Denmark and Germany and for Buprenorphine 200 microgram and 400 microgram Sublingual Tablets in Germany.

Buprenorphine 200 microgram and 400 microgram Sublingual Tablets are indicated as a strong analgesic for the relief of severe pain, e.g. following surgery or injuries, myocardial infarction and in cancer. Use of Buprenorphine 200 microgram and 400 microgram Sublingual Tablets is NOT indicated in the treatment of headache, toothache, migraine or other conditions involving pain which can be treated using peripherally active analgesics and/or spasmolytics.

The active ingredient, buprenorphine, belongs to the pharmacotherapeutic group of 'potent analgesics, partial opioid receptor agonists' (ATC code – N02AE01). Buprenorphine is a potent, centrally active analgesic with opioid-agonistic and opioid-antagonistic properties. The analgesic effect is attributable to interaction with specific opioid receptors (mainly μ -receptors) in the central nervous system. The long duration of effects (6 – 8 hours) is attributed to the slow rate of dissociation of buprenorphine from receptors and the limited extent to which the effects are counteracted by morphine antagonists because of the high affinity of buprenorphine for the receptor.

Buprenorphine can induce a fall (or rarely, also an increase) in heart rate and blood pressure and also has antitussive and respiratory depressive effects. If buprenorphine is administered after pure opioid agonists, its antagonistic effects may be manifested dependent on the dose

administered, i.e. the effects of the agonists, such as morphine, may be attenuated or abolished.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by two bioequivalence studies comparing the pharmacokinetic profiles of the test products, Buprenorphine 200 microgram and 400 microgram Sublingual Tablets, to those of Temgesic 0.2 mg and Temgesic forte 0.4 mg sublingual tablets, sourced from the EU (Essex Pharma GmbH, Germany). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	UK/H/1943/001-2/DC - PL 04416/0956-57 - Tephine 200 microgram and 400 microgram Sublingual Tablets UK/H/1944/001-2/DC - PL 04416/0958-59 - Buprenorphine 200 microgram and 400 microgram Sublingual Tablets UK/H/1945/001-2/DC - PL 04416/1169-70 - Buprenorphine 200 microgram and 400 microgram Sublingual Tablets
Name(s) of the active substance(s) (INN)	Buprenorphine
Pharmacotherapeutic classification (ATC code)	Potent analgesic, partial opioid receptor agonist (N02AE01)
Pharmaceutical form and strength(s)	Sublingual tablets 200 microgram and 400 microgram
Reference numbers for the Decentralised Procedure	UK/H/1943/001-2/DC UK/H/1944/001-2/DC UK/H/1945/001-2/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/1943/001-2/DC: DE and DK UK/H/1944/001-2/DC: DE UK/H/1945/001-2/DC: DE
Marketing Authorisation Number(s)	PL 04416/0956-957 PL 04416/0958-959 PL 04416/1169-1170
Name and address of the authorisation holder	Sandoz Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Buprenorphine Hydrochloride

Nomenclature:

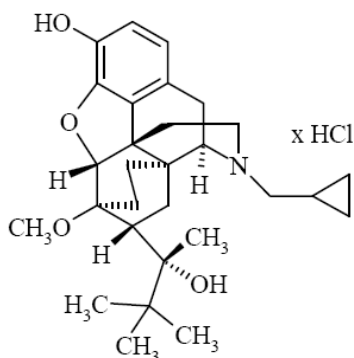
INN: Buprenorphine Hydrochloride

Chemical names: i) (5*R*,6*R*,7*R*,9*R*,13*S*,14*S*)-17-Cyclopropylmethyl-7-[(*S*)-3,3-dimethyl-2-hydroxybutan-2-yl]-6-methoxy-4,5-epoxy-6,14-ethanomorphinan-3-ol

ii) (2*S*)-2-[17-(cyclopropylmethyl)-4,5*α*-epoxy-3-hydroxy-6-methoxy-6*α*,14-ethano-14*α*-morphinan-7*α*-yl]-3,3-dimethylbutan-2-ol hydrochloride

CAS Registry name: [5*α*,7*α*(*S*)]-17-(cyclopropylmethyl)-*α*-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-*α*-methyl-6,14-ethenomorphinan-7-methanol hydrochloride

Structure:



Molecular formula: C₂₉H₄₁NO₄ · HCl

Molecular weight: 504.1 g/mol

CAS No: 53152-21-9

Physical form: White to almost white, crystalline powder

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

The active substance, buprenorphine hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur) monograph.

All aspects of the manufacture and control of buprenorphine hydrochloride are supported by European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability (CEPs). The certificates are accepted as confirmation of the suitability of buprenorphine hydrochloride for inclusion in these medicinal products.

Stability studies have been performed with the drug substance and no significant changes of the parameters were observed. The retest period proposed is supported by satisfactory information.

MEDICINAL PRODUCT

Description and Composition

Buprenorphine 200 microgram and 400 microgram Sublingual Tablets are presented as white to off-white, round (200 microgram strength) and oval-shaped (400 microgram strength) tablets. Each tablet contains 200 microgram or 400 microgram of the active ingredient, buprenorphine, as buprenorphine hydrochloride.

Other ingredients consist of pharmaceutical excipients, namely citric acid anhydrous, lactose monohydrate, mannitol, sodium citrate, sodium stearyl fumarate and pregelatinised starch (maize). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to develop physically and chemically stable, sublingual tablet formulations of buprenorphine 200 microgram and 400 microgram, bioequivalent to the reference products, Temgesic 200 microgram and 400 microgram Sublingual Tablets.

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. Satisfactory commitments have also been provided to validate additional full scale production batches.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Buprenorphine 200 microgram and 400 microgram Sublingual Tablets are licensed for marketing in polyvinylchloride (PVC) - polyvinylidene chloride (PVdC) - aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 7, 10, 20, 24, 28, 30, 48, 50 and 70. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 18 months. These medicinal products do not require any special storage conditions.

Quality Overall Summary

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The user-testing of the PIL text has been evaluated and is accepted. The labelling fulfils the statutory requirements for Braille.

For Tephine 200 microgram and 400 microgram Sublingual Tablets (PLs 04416/0956-57), satisfactory mock-ups of the PIL and labelling have been provided. The labelling fulfils the statutory requirements for Braille.

For Buprenorphine 200 microgram and 400 microgram Sublingual Tablets (PLs 04416/0958-9 and 1169-70), the MAH has submitted text versions only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. Commitments have also been made to register an appropriate invented name.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Buprenorphine 200 microgram and 400 microgram Sublingual Tablets from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of buprenorphine, a widely used and well-known active substance. The overview, dated September 2009, cites 55 references from the published literature dated up to year 2009. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK products, Temgesic 200 microgram and 400 microgram Sublingual Tablets (PL 36699/0001-3, RB Pharmaceuticals Limited).

There are no objections to approval of Buprenorphine 200 microgram and 400 microgram Sublingual Tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Buprenorphine 200 microgram and 400 microgram Sublingual Tablets are indicated as a strong analgesic for the relief of severe pain, e.g. following surgery or injuries, myocardial infarction and in cancer. Use of Buprenorphine 200 microgram and 400 microgram Sublingual Tablets is NOT indicated in the treatment of headache, toothache, migraine or other conditions involving pain which can be treated using peripherally active analgesics and/or spasmolytics.

The indications are consistent with those for the reference products and are satisfactory.

POSODOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of buprenorphine is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of buprenorphine is well-known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence studies

The applications are supported by 2 bioequivalence studies presented by the applicant comparing the pharmacokinetic profiles of the test products, Buprenorphine 200 microgram and 400 microgram Sublingual Tablets, to those of Temgesic 0.2 mg and Temgesic forte 0.4 mg sublingual tablets, sourced from the EU (Essex Pharma GmbH, Germany). SUBUTEX 0.4 mg sublingual tablets, sourced from the EU (Essex Pharma GmbH, Germany), was used as an additional reference product in the 0.4 mg strength biostudy.

The studies were of an appropriate design and were conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products. The UK reference products, Temgesic 200 microgram and 400 microgram Sublingual Tablets (PL 36699/0001-3, RB Pharmaceuticals Limited), are considered to be equivalent to the clinical reference products, Temgesic 0.2 mg and Temgesic forte 0.4 mg sublingual tablets, sourced from Europe and used in the bioequivalence study.

Prior to dosing, subjects were given 3 mL of water to moisten their mouth and instructed to swallow it immediately before dosing. One sublingual tablet, either the test or reference, was placed in the mouth under the tongue by the study personnel. Subjects were instructed to let the tablet melt and were told not to chew, swallow, crush or move the tablet around on the floor of the mouth or from under the tongue. Subjects were instructed to avoid swallowing until the tablet had dissolved.

Each dose of study medication was administered following pre-medication with a 100 mg naltrexone tablet given 2 hours prior to the study medication, swallowed with 240ml of water. In order to detect any opioid dependence among prospective subjects, a naltrexone challenge test was performed on the day before buprenorphine dosing (Day -1) in Period 1. During Period 1, anyone who failed the naltrexone challenge was replaced by a stand-by before buprenorphine administration.

The primary pharmacokinetic parameters for the studies were C_{max} and AUC_{0-t} . Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max} and AUC_{0-t} for buprenorphine.

Study A – 0.2 mg, fasted

This was an open-label, randomised, two-period, two-sequence, two-treatment crossover bioequivalence study conducted in healthy adult male subjects under fasting conditions.

The volunteers were randomised to receive a dose of 0.4 mg (2 x 0.2 mg) of either the applicant's test product or the reference product buprenorphine sublingual tablets.

Blood samples were taken pre-dose (0.0) and at specified time points up to 60.0 hours after administration of test or reference product. Plasma levels of buprenorphine were quantified by a validated LC/MS-MS bioanalytical method. A satisfactory washout period of 21 days was maintained between the dosing days in each group.

Results:

A sufficient number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of any subjects was satisfactorily justified.

Safety - There were no deaths or serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated below.

Pharmacokinetic results for buprenorphine for a randomised, two-period, two-treatment crossover study; healthy subjects, dosed fasted; $t=60$ hours; wash-out period: 21 days. Buprenorphine 200 mcg Sublingual Tablets vs. Temgesic 0.2 mg sublingual tablets

Parameters	Geometric Least Squares Mean	90% CI (Parametric)
	Ratio %	
C_{max} (ng/ml)	92.36	83.40-102.28%
AUC_{0-t} (ng.h/ml)	93.01	84.91-101.89%
C_{max}	maximum plasma concentration	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours	

Conclusion

Bioequivalence has been demonstrated between the test and reference products for a study of the 0.2 mg strength tablets, conducted under fasting conditions.

Study B – 0.4 mg, fasted

This was an open-label, randomised, three-sequence, three-way, single-dose crossover bioequivalence study conducted in healthy adult male subjects under fasting conditions. The reference products were SUBUTEX 0.4 mg sublingual tablets (Reference product 1) and Temgesic forte 0.4 mg sublingual tablets (Reference product 2).

The volunteers were randomised to receive a single dose of 0.4 mg of either the applicant's test product or one of two reference product buprenorphine sublingual tablets.

Blood samples were taken pre-dose (0.0) and at specified time points up to 60.0 hours after administration of test or reference product. Plasma levels of buprenorphine were quantified by a validated LC/MS-MS bioanalytical method. A satisfactory washout period of 21 days was maintained between the dosing days in each group.

Results:

A sufficient number of subjects were enrolled in the study; all subjects completed the 'test product vs. Reference product 1' study and were included in the pharmacokinetic evaluation and statistical analysis; all but one of the subjects completed the 'test product vs. Reference product 2' study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 1 subject was satisfactorily justified.

Safety - There were no deaths or serious or significant adverse events reported in the study.

The summary of the results of the bioequivalence study are tabulated below.

Pharmacokinetic results for buprenorphine for a randomised, three-sequence, three-way, single-dose crossover study; healthy subjects, dosed fasted; t=60 hours; wash-out period: 21 days. Buprenorphine 400 mcg Sublingual Tablets vs. SUBUTEX 0.4 mg sublingual tablets

Parameters	Geometric Least Squares Mean	90% CI (Parametric)
	Ratio %	
C_{max} (ng/ml)	99.00	85.95-114.04%
AUC_{0-t} (ng.h/ml)	103.59	90.23-118.93%
C _{max} maximum plasma concentration AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours		

Buprenorphine 400 mcg Sublingual Tablets vs. Temgesic forte 0.4 mg sublingual tablets

Parameters	Geometric Least Squares Mean	90% CI (Parametric)
	Ratio %	
C_{max} (ng/ml)	104.68	90.73-120.77%
AUC_{0-t} (ng.h/ml)	108.21	94.11-124.42%
C _{max} maximum plasma concentration AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours		

Conclusion

Bioequivalence has been demonstrated between the test and reference products for a single-dose study of the 0.4 mg strength tablets, conducted under fasting conditions.

Discussion on Bioequivalence

The results of the bioequivalence studies show that Buprenorphine 200 microgram Sublingual Tablets are bioequivalent to Temgesic 0.2 mg sublingual tablets, and Buprenorphine 400 microgram Sublingual Tablets are bioequivalent to SUBUTEX 0.4 mg sublingual tablets and Temgesic forte 0.4 mg sublingual tablets, as the confidence intervals for C_{max} and AUC_{0-t} for buprenorphine fall within the acceptance criteria ranges of 80-125%, in line with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CPMP/EWP/QWP/1401/98).

Clinical efficacy

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of buprenorphine is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of buprenorphine is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those of the UK reference products and are acceptable.

Patient Information Leaflet

The final PIL texts are in line with the approved SmPCs and are satisfactory. The PIL user-testing has been evaluated and is accepted.

Labelling

The labelling is satisfactory.

Clinical overview

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The overview, dated September 2009, cites 72 references from the published literature dated up to year 2009. The CV of the clinical expert has been supplied.

CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was recommended on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Buprenorphine 200 microgram and 400 microgram 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.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

The applicant's Buprenorphine 200 microgram Sublingual Tablets has been demonstrated to be bioequivalent to Temgesic 0.2 mg sublingual tablets. The applicant's Buprenorphine 400 microgram Sublingual Tablets has been demonstrated to be bioequivalent to SUBUTEX 0.4 mg sublingual tablets and Temgesic forte 0.4 mg sublingual tablets. The UK reference products, Temgesic 200 microgram and 400 microgram Sublingual Tablets (PL 36699/0001-3, RB Pharmaceuticals Limited), are considered to be equivalent to the clinical reference products, Temgesic 0.2 mg and Temgesic forte 0.4 mg sublingual tablets, sourced from Europe.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs are consistent with those of the UK reference products and are satisfactory. The approved Patient Information Leaflet (PIL) and labelling texts are satisfactory. The labelling fulfils the statutory requirements for Braille.

For Tephine 200 microgram and 400 microgram Sublingual Tablets (PLs 04416/0956-57), satisfactory mock-ups of the PIL and labelling have been provided. The PIL has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. The approved labelling artwork complies with statutory requirements. In line with current legislation, the names of the products in Braille appear on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

For Buprenorphine 200 microgram and 400 microgram Sublingual Tablets (PLs 04416/0958-9 and 1169-70), the MAH has submitted text versions only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's Buprenorphine 200 microgram and 400 microgram Sublingual Tablets are generic versions of Temgesic 200 microgram and 400 microgram Sublingual Tablets (RB Pharmaceuticals Limited). Extensive clinical experience with buprenorphine is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome