SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tephine 200 microgram Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 microgram of buprenorphine (as buprenorphine hydrochloride).

Excipient(s) with known effect
Each tablet contains 42.7 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet.

White to off-white, round, biplane tablet with facet (diameter: approximately 5.00 mm).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Use of Tephine 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

Posology

Adults
The dose of Tephine should generally be adjusted to the intensity of the pain and the individual sensitivity of the patient.

The recommended single dose in patients with a bodyweight greater than 45 kg is 1 – 2 sublingual tablets of Tephine 200 microgram

The onset of effects generally occurs within 30 minutes after sublingual administration.
The average duration of effects is 6 – 8 hours.
If necessary, 1 – 2 sublingual tablets of Tephine 200 microgram may be administered every 6 – 8 hours.

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

Children
Patients with a bodyweight of more than 37.5kg and capable of using a sublingual tablet may start treatment with a single dose of 1 sublingual tablet of Tephine 200 microgram, if necessary, every 6 – 8 hours.

Buprenorphine should not be used in children weighing less than 37.5 kg.

Renal impairment
Caution is recommended in patients with severe renal insufficiency (creatinine clearance < 30 ml/min).

Hepatic impairment
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 in this patient group.
Buprenorphine is contraindicated in patients with severe hepatic impairment (see section 4.3)

Method of administration
The sublingual tablets are placed under the tongue, where they will dissolve within 5 – 10 minutes. If the oral mucosa is very dry, 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.

Treatment goals and discontinuation

Before initiating treatment with Tephine, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with Tephine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of use
Tephine 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 dose Tephine should continue to be administered.
There is currently insufficient clinical experience of longer term use of buprenorphine in children.

4.3 Contraindications

- Hypersensitivity to the active substance, centrally acting analgesics or to any of the excipients listed in section 6.1
- Opioid-dependent patients and for drug-substitution treatment
- Severe respiratory insufficiency
- Severe hepatic impairment

4.4 Special warnings and precautions for use

Respiratory depression
As with other potent opioids, clinically significant respiratory depression may occur in patients receiving buprenorphine within the therapeutic dose range. Buprenorphine should be used with caution in patients with impaired respiratory function (e.g. in chronic obstructive pulmonary disease, asthma cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression). Particular caution should be exercised if buprenorphine is administered to patients who receive or have recently received medicinal products with CNS / respiratory impairment. Patients with the above mentioned physical and / or pharmacological risk factors should be monitored and dose reduction should be considered.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products
Concomitant use of buprenorphine and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe buprenorphine

concomitantly with sedative medicinal products the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Serotonin syndrome
Concomitant administration of buprenorphine and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tephine. Repeated use of Tephine can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Tephine may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Tephine and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Dependency
Buprenorphine is a partial agonist at the μ-opiate receptor and chronic administration produces dependence of the opioid type. Buprenorphine has certain opioid properties that can lead to an opioid-like euphoria.

Controlled human and animal studies indicate that buprenorphine has a substantially lower dependence liability than pure agonist analgesics, such as morphine.

Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset. Withdrawal symptoms include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal disorders.

Buprenorphine should be used to relieve pain and not as preventive treatment.

In susceptible patients dependence may lead to self-administration of the medicinal product although pain no longer exists. Patients should not exceed the prescribed dose and it is strongly advised to contact their physician if other prescription medicinal products are administered concurrently or in the future.

Use in opioid-dependent patients
Buprenorphine analgesics may cause withdrawal symptoms in opioid-dependent patients receiving pure agonist analgesics such as methadone or heroin. Accordingly, caution should be exercised when prescribing buprenorphine to patients who are known to be drug addicted or with a history of drug abuse.

Minor euphoric effects of buprenorphine have been observed in humans. This could result in abuse of the substance to some extent. The current level of dependence should be evaluated in patients with opioid addiction or abuse prior to initiation of treatment with buprenorphine.

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.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine was evaluated in a post-marketing study. Since buprenorphine is extensively metabolised hepatically, plasma levels were found to be higher in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Buprenorphine should be used with caution in patients with moderate hepatic impairment. The use of buprenorphine is contraindicated in patients with severe hepatic impairment (see section 4.3).

Buprenorphine, like other opioids, has been shown to increase the pressure in the bile duct, thus caution is required in patients with biliary tract disorders.

Renal impairment
Renal elimination may be prolonged since 30% of the administered dose is eliminated by the renal route. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min).

Cardiovascular effect

Buprenorphine may cause a slight reduction in pulse rate and blood pressure in some patients. Like other opioids, buprenorphine may produce orthostatic hypotension in ambulatory patients.

Head injury and increased intracranial pressure
Opioids may elevate cerebrospinal fluid pressure, so opioids should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. 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.

Acute abdominal conditions
As with other μ-opiate receptor agonists, the administration of buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

General warnings relevant to the administration of opioids
Particular careful monitoring is required in:

- myxoedema or hypothyroidism
- adrenal insufficiency (e.g. Addison's disease)
- central nervous system depression or coma
- toxic psychosis
- prostatic hypertrophy or ureteral stenosis
- acute alcoholism
- delirium tremens
- kyphoscoliosis with restrictive airways disorders
- myasthenia gravis
- elderly and debilitated patients or in patients who have recently been treated with narcotic analgesics

The concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine (see section 4.5).

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dose.

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

Tephine contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, , total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per sublingual tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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. Since the hepatic elimination plays a relatively large role (~70%) in the clearance of buprenorphine, lower initial doses and careful dose titration may be required when anaesthetics such as halothane are co-administered.

Buprenorphine should be used cautiously when co-administered with:
Alcoholic drinks or medicinal products containing alcohol
Buprenorphine should not be taken together with alcoholic drinks or medicinal products containing alcohol. Alcohol increases the sedative effect of buprenorphine (see section 4.7).

Sedative medicinal products such as benzodiazepines or related medicinal products
The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Other central nervous system depressants
Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machines hazardous. Central nervous system depressants include other opioid derivatives (e.g. methadone, analgesics and antitussives), anaesthetics, phenothiazine, other tranquilizer and sedative hypnotics, certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, anticholinergics, clonidine and related substances. The concomitant use of buprenorphine with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Concomitant administration of buprenorphine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

Naltrexone
Naltrexone is an opioid antagonist that can block the pharmacological effects of buprenorphine. For patients who have developed physical dependence of buprenorphine, co-administration with naltrexone should be avoided due to the potential interaction that prevents the intended analgesic effect and may abruptly induce opioid withdrawal symptoms.

Other opioid analgesics
The analgesic effect of full opioid agonists can be reduced by the partial agonist buprenorphine due to competitive receptor block. For patients who have developed

physical dependence of full opioid agonists, administration of the partial agonist buprenorphine may induce withdrawal syndrome (see section 4.4).

CYP3A4 inhibitors
Since the metabolism of buprenorphine is mediated by the CYP3A4 isoenzyme, co-administration of medicinal products that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine.

In a study of the interactions of buprenorphine with ketoconazole, elevated concentrations of buprenorphine and norbuprenorphine were measured. Thus, patients receiving buprenorphine co-administered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g. erythromycin), azole antifungal agents (e.g. ketoconazole) gestodene, triacetyloleandomycin, or protease inhibitors (e.g. ritonavir, indinavir, saquinavir and atazanavir) should be closely monitored. Caution is advised when administering buprenorphine to patients receiving these medicinal products, and if necessary dose adjustments should be considered.

CYP3A4 inducers
CYP3A4 inducers (e.g. phenobarbital, rifampicin, carbamazepine, and phenytoin) induce metabolism and thus lead to increased clearance of buprenorphine. Caution is advised when administering buprenorphine to patients receiving these medicinal products, and if necessary, dose adjustments should be considered.

Monoamine oxidase inhibitors (MAOIs)
Possible exaggeration of the effects of opioids, based on experience with morphine (see section 4.4).

Serotonergic medicinal products
Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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

To date, no notable interaction has been observed with cocaine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data on the use of buprenorphine during pregnancy.

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.

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 woman, the foetus and the neonate by the physician is essential.

Breast-feeding
As buprenorphine and its metabolites are excreted in human milk, buprenorphine should not be administered during breast-feeding.

Fertility
No human data on fertility are available. No undesirable effects on fertility or general reproductive potential have been observed in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - o The medicine has been prescribed to treat a medical or dental problem and
    - o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - o It was not affecting your ability to drive safely.

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

Summary of the safety profile
The most commonly reported adverse reactions in clinical studies were sedation, vertigo, dizziness and nausea.

Tabulated list of adverse events
The evaluation of undesirable effects is based on the following frequency conventions:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

Table 1. Adverse drug reactions reported in clinical studies and / or post marketing studies

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders				Hypersensitivity	Anaphylactic shock[1]
Metabolism and nutrition disorders				Decreased appetite	
Psychiatric disorders			Confusion Euphoria Disorientation Nervousness Depression Psychosis Hallucinations Depersonalisation	Dysphoria Agitation	Drug dependence
Nervous system Disorders	Sedation Dizziness Tiredness Insomnia	Headache	Dysarthria Paraesthesia Coma Tremor Exhaustion Slurred speech Lack of muscle coordination	Seizures Coordination abnormal	Somnolence
Eye disorders		Miosis	Vision blurred Diplopia Visual impairment Conjunctivitis		
Ear and labyrinth disorders	Vertigo		Tinnitus		

System Organ Class	Very Common	Common	Uncommon	Rare	Not known
Cardiac disorders			Tachycardia Bradycardia Cyanosis Atrioventricular block second degree		
Vascular disorders		Hypotension	Hypertension Pallor		
Respiratory, thoracic and mediastinal disorders		Hypoventilation	Dyspnoea Apnoea		Respiratory depression Bronchospasm
Gastrointestinal disorders	Nausea	Vomiting	Dry mouth Constipation Dyspepsia Flatulence	Diarrhoea	Dental caries
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritus Rash	Urticaria	Angioedema (Quincke‘s oedema)[1]
Renal and urinary disorders			Micturition disorders Urinary retention		
General disorders and administration site conditions			Asthenia Fatigue Malaise Flushing		Drug ineffective Drug interactions

[1] Adverse reactions reported post-marketing with less than 1% but included because they are serious.

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 the development of mouth ulcers and haemorrhagic diathesis) can occur after use of buprenorphine sublingual tablets.

Drug dependence
Repeated use of Tephine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Buprenorphine appears to have a wide margin of safety because of its partial opioid agonist/ antagonist properties.

Even doses in the therapeutic range may cause serious poisoning (intoxication) in subjects who are hypersensitive (particularly children).
Even if the antagonistic activity of buprenorphine may manifest at doses slightly higher than the recommended therapeutic range, under certain circumstances doses within the recommended therapeutic range may cause a clinically significant respiratory depression (see section 4.4).

Symptoms
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 miosis, sedation, hypotension, respiratory depression, (reduced respiratory rate and/or respiratory volume, Cheyne-Stokes respiration, cyanosis), extreme sleepiness, disturbance of consciousness with coma in extreme cases, relaxation of the skeletal muscles, moist-cold skin and bradycardia.
Nausea and vomiting may occur.
The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

Treatment:
In case of an overdose, general supportive treatment, including close monitoring of patient respiratory and cardiac status, should be initiated. Symptomatic treatment of respiratory depression should be initiated following standard intensive care. Ensure that there is open airways as well as assisted or controlled ventilation. The patient should be transferred to facilities where complete resuscitation equipment is available. If patient vomits, take care to prevent aspiration from vomiting.

An opioid antagonist (i.e. naloxone) is recommended, although it may have a modest effect on the buprenorphine-induced respiratory symptoms compared to its effect on complete

opioid agonists. As naloxone does not necessarily reverse the buprenorphine-induced respiratory depression, the primary treatment of overdose should consist in restoring adequate ventilation, if mechanically assisted respiration required.

Buprenorphine's long duration of action should be considered when deciding how long it is necessary to provide treatment to reverse the effects of an overdose. Naloxone can be cleared faster than buprenorphine, whereby the overdose symptoms so far controlled can return. High doses may be required, either as a repeated bolus or infusion (for example starting with an intravenous bolus injection of 1-2 mg). Once a sufficient antagonistic effect is achieved, it is advised to administer naloxone via infusion to maintain constant plasma levels of naloxone

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids, Oripavine derivatives 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 depressant 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.

Pain relief occurs within 30 minutes after sublingual use and the effect lasts at least 4 hours.

5.2 Pharmacokinetic properties

Absorption
Buprenorphine is well absorbed after sublingual administration. 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.

Distribution
Following intravenous injection of buprenorphine, plasma concentrations fall rapidly in the initial phase with a half-life of 2 – 5 minutes (distribution phase). The concentrations of the active substance 10 minutes after i.m. injection are equivalent to those after i.v. injection.
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.

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.

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.

The terminal half-life is approximately 3 hours. Terminal half-life after i.m. administration is also 3 hours.

Pharmacokinetic/pharmacodynamic relationship
Because of the persistent receptor binding, pharmacodynamic effects do not correlate with blood concentrations or the elimination half-life of buprenorphine.

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 post-implantation 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 and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0956

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/09/2011

10 DATE OF REVISION OF THE TEXT

31/10/2024