SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Buprenorphine G. L. Pharma, 0.2 mg sublingual tablets
Buprenorphine G. L. Pharma, 0.4 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<INVENTED NAME> 0.2 mg sublingual tablets
Each sublingual tablet contains 0.2 mg buprenorphine (equivalent to 0.216 mg buprenorphine hydrochloride).
<INVENTED NAME> 0.4 mg sublingual tablets
Each sublingual tablet contains 0.4 mg buprenorphine (equivalent to 0.432 mg buprenorphine hydrochloride).

Excipient with known effect
<INVENTED NAME> 0.2 mg: one tablet contains 29.844 mg lactose monohydrate.
<INVENTED NAME> 0.4 mg: one tablet contains 29.628 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

<INVENTED NAME> 0.2 mg sublingual tablets are white to off-white, round, biconvex tablets, debossed with “I” on one side, with a diameter of approximately 5 mm.

<INVENTED NAME> 0.4 mg sublingual tablets are white to off-white, round, biconvex tablets, plane on both sides, with a diameter of approximately 5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<INVENTED NAME> is used for the treatment of severe postoperative pain in adults.

4.2 Posology and method of administration

Posology

In general, the dosage of <INVENTED NAME> should always be adjusted to patient’s pain and individual sensitivity.

Because the analgesic effect starts slowly, these sublingual tablets are not suitable for the treatment of acute pain. Treatment should therefore be initiated with, for example, the parenteral form of buprenorphine. Treatment can then be continued with the sublingual form. Recommended dose is 0.2–0.4 mg, every 6-8 hours as needed.

Duration of use

<INVENTED NAME> should not be used for more than 6-7 days. If prolonged pain management is required, regular checks should be made at short intervals (if necessary, with breaks in treatment) to establish whether, and at which dose. < INVENTED NAME> should not be used longer than necessary.

Treatment control
Respiratory depression can be partially reversed with naloxone. In more severe cases, assisted breathing should be considered.

Specific patient groups

Patients with hepatic insufficiency
Buprenorphine is metabolised in the liver. Plasma levels are elevated in moderate and severe hepatic impairment compared to healthy subjects (see section 5.2). <INVENTED NAME> should be used with caution in patients with moderate hepatic impairment. Lower initial doses and careful dose titration may be required. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased buprenorphine levels (see section 4.4). <INVENTED NAME> is contraindicated in patients with severe hepatic impairment (see section 4.3).

Patients with renal insufficiency
As buprenorphine is eliminated primarily through hepatic metabolism, no dose adjustment in patients with mild renal impairment is necessary. However, caution is advised for patients with severe renal insufficiency (see section 4.4)

Paediatric patients
<INVENTED NAME> is not recommended for use in children due to insufficient data on safety and efficacy.

Elderly
A single dose of 0.2 mg is sufficient in most cases. In some cases (e.g. elderly patients with liver impairment) the dose should be reduced and gradually adjusted according to the patient response.

Method of administration

For sublingual use only.
The sublingual tablets must not be sucked, chewed or swallowed.
The tablets cannot be divided.

The sublingual tablets are placed under the tongue, where they dissolve within 5 to 10 minutes. In patients with very dry oral mucosa, a few drops of liquid can accelerate the disintegration process.

Treatment goals and discontinuation
Before initiating treatment with <INVENTED NAME>, 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 <INVENTED NAME>, 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).

4.3 Contraindications

<INVENTED NAME> must not be used in the following cases:
- hypersensitivity to buprenorphine, centrally acting analgesics or to any of the excipients listed in

section 6.1,
- severe respiratory insufficiency,
- severe hepatic insufficiency
- acute alcoholism or delirium tremens

4.4 Special warnings and precautions for use

Risks of co-administering sedatives, such as benzodiazepines or related medicinal products

Concomitant use of <INVENTED NAME> and sedative agents such as benzodiazepines or related medicinal products can lead to sedation, respiratory depression, coma and death. Based on these risks, concomitant prescription with such sedatives is indicated only in those patients for whom there are no alternative treatment options. Nevertheless, if concomitant prescription of <INVENTED NAME> together with sedatives is deemed necessary, the lowest effective dose should be used and the duration of treatment should be as short as possible. Patients should be closely monitored for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers about these symptoms (see section 4.5).

Respiratory depression

As with other potent opioids, clinically significant respiratory depression may occur within the recommended dose range in patients on therapeutic doses of buprenorphine. This medicine must be used with caution in patients with impaired respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression). Particular caution is advised when buprenorphine is administered to patients currently taking or recently using medicinal products with a centrally depressant/respiratory depressant effect (see section 4.5). Monitoring is required for patients with physical and/or the above-mentioned pharmacological risk factors and a dose reduction may be considered.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea and sleep-related hypoxaemia. Opioid use is associated with a dose-dependent increase in the risk of central sleep apnoea. In patients with central sleep apnoea, a reduction of the total opioid dose should be considered.

Serotonin syndrome

Concomitant use of <INVENTED NAME> with other serotonergic medicinal products such as MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants may lead to a serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic medicinal products is clinically indicated, careful observation of the patient is recommended, particularly at the start of treatment and when increasing the dose.
Symptoms of serotonin syndrome include, but are not limited to, mood changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of treatment should be considered, depending on the severity of 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 <INVENTED NAME>. Repeated use of <INVENTED NAME> 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 <INVENTED NAME> 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 <INVENTED NAME> 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.

Use in opioid-dependent patients

Buprenorphine-containing analgesics may induce withdrawal symptoms in opioid-dependent patients receiving full opioid agonists such as methadone or heroin.
Similarly, as an analgesic, buprenorphine should only be prescribed with caution in known abusers or in patients with a history of opioid dependence.

Impaired hepatic function

In a post-marketing study, the effect of hepatic impairment on the pharmacokinetics of buprenorphine was investigated. As buprenorphine is predominantly metabolised in the liver, elevated plasma levels have been found in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased buprenorphine concentrations.
Buprenorphine should be used with caution in patients with impaired hepatic function. In patients with severe hepatic insufficiency, the use of buprenorphine is contraindicated.

Buprenorphine has been shown to increase pressure in the biliary tract to a similar extent as other opioid analgesics; it must therefore be administered with caution in patients with biliary tract disorders.

Renal impairment

Excretion via the kidneys may be prolonged, as approximately 30% of the given dose is excreted via the kidneys. Accumulation of buprenorphine metabolites occurs in patients with renal insufficiency. Particular caution is indicated in the treatment of patients with impaired renal function or severe renal insufficiency (CL_{cr} < 30 mL/min).

Cardiovascular effects

In some patients, buprenorphine can cause a slight reduction in the pulse rate and blood pressure. Like other opioids, buprenorphine may cause orthostatic hypotension in ambulant patients.

Head injuries and increased intracranial pressure

Like other potent opioids, buprenorphine may possibly increase cerebrospinal fluid pressure and should be used with caution in patients with head injuries, intracranial lesions and other conditions with a possible increase in cerebrospinal fluid pressure. This effect in combination with the respiratory depressant effect may be significantly increased in patients with head injuries. As buprenorphine can also cause miosis and changes in the state of consciousness, clinical progression in patients with head injuries may be masked and assessment of the clinical picture may be confounded.

Acute abdominal disorders

As with other μ-opioid receptor agonists, administration of buprenorphine can mask diagnosis and progression in patients with acute abdominal disorders.

General warnings for the opioid class of medicines

In patients with the following disorders, particularly careful medical surveillance is required:

- myxoedema or hypothyroidism,
- adrenocortical insufficiency (e.g. Addison's disease),
- CNS depression or coma,
- toxic psychosis,
- prostatic hypertrophy or ureteral stenosis,
- kyphoscoliosis with restrictive airway disease,
- caution in elderly or debilitated patients and in patients recently treated with narcotic analgesics.

<INVENTED NAME> contain lactose monohydrate and sodium. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

This medicine 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

Serotonergic medicinal products

Serotonergic medicinal products such as MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants, as the risk of a serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).The risk of serotonin syndrome is low with buprenorphine but it has been observed with other opioids.

Sedatives, such as benzodiazepines or related medicinal products

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

Alcoholic beverages or medicinal products containing alcohol

Buprenorphine should not be taken together with alcoholic beverages or medicinal products containing alcohol. The sedative effect of buprenorphine is potentiated by alcohol (see section 4.7).

Other central nervous system depressants

If taken together with buprenorphine, the depressant effect on the central nervous system may be increased. The reduced level of attentiveness may make it dangerous to drive vehicles and use machines.
Central nervous system depressants include other opioid derivatives (such as methadone, analgesics, antitussives), anaesthetics, phenothiazines, other tranquillisers and sedative hypnotics, certain antidepressants, sedative H_1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. When such drug combinations are considered, it is important that the dose of one or both drugs be reduced.
The concomitant use of <INVENTED NAME> with other central nervous system depressants, and 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. In patients who have developed a physical dependence on buprenorphine, concomitant use of naltrexone and buprenorphine should be avoided due to the potential interaction that prevents effective pain management and may lead to sudden onset of opioid withdrawal symptoms.

Other opioid analgesics

The antinociceptive effect of full agonist opioids might be impaired by the partial agonist buprenorphine, as a result of competitive receptor blockade.
In patients who have developed a physical dependence on full agonists, administration of the partial agonist buprenorphine might induce withdrawal symptoms (see also "Use in opioid-dependent patients", section 4.4).

CYP3A4 inhibitors

As buprenorphine metabolism occurs via the isozyme CYP3A4, concomitant administration of CYP3A4 inhibitors might lead to reduced clearance of buprenorphine. In an interaction study with buprenorphine and ketoconazole, elevated concentrations of buprenorphine and norbuprenorphine were measured. Close monitoring is therefore required in patients receiving buprenorphine concomitantly with CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin), azole-type antifungals (e.g. ketoconazole), gestodene, triacetyloleandomycin or HIV-protease inhibitors (e.g. ritonavir, indinavir, saquinavir and atazanavir). Caution is advised when administering <INVENTED NAME> to patients using these medicinal products and, if necessary, dose adjustments should be considered.

CYP3A4 inducers

CYP3A4 inducers, such as phenobarbital, rifampicin, carbamazepine and phenytoin, induce the metabolism and may lead to increased clearance of buprenorphine. Caution is advised when administering <INVENTED NAME> to patients using these medicinal products and, if necessary, dose adjustments should be considered.

Monoamine oxidase inhibitors (MAO inhibitors)

Based on experience with morphine, the effect of opioids may be potentiated (see section 4.4).
In patients previously treated with certain antidepressants (MAO inhibitors) within the last 14 days prior to opioid use, there is a theoretical possibility of life-threatening interactions affecting the brain, breathing and blood circulation functions. Such combinations should be avoided for up to 2 weeks after discontinuation of MAO inhibitors.

In one case, a possible interaction between intravenous <INVENTED NAME> and phenprocoumon, leading to purpura, was reported.

Additional
A decrease in hepatic perfusion, which may be induced by certain general anaesthetics (e.g. halothane) and other medicinal products, may slow the hepatic elimination of buprenorphine. As hepatic elimination plays a relatively major role (~ 70%) in the overall clearance of buprenorphine, lower initial doses and careful dose titration may be required during use in conjunction with anaesthetics such as halothane.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of buprenorphine in pregnant women. Low-dose buprenorphine preparations must not be used during pregnancy unless the clinical condition of the woman requires treatment with buprenorphine. In such cases, the pregnant woman, fetus and newborn

infant must be closely monitored by the physician.

Towards the end of pregnancy, administration of high doses may lead to neonatal respiratory depression even after a short period of use.

During the last trimester of pregnancy, chronic use of buprenorphine may be responsible for neonatal withdrawal syndrome.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

When used as directed, buprenorphine has minor or moderate influence on the ability to drive and use machines. This medicinal product can impair the mental or physical abilities and cause drowsiness, dizziness or impaired thinking, especially upon initiation of therapy and dose adjustment. Patients must be warned accordingly.
This effect may be potentiated if buprenorphine is co-administered with alcohol or agents with a depressant effect on the central nervous system (see sections 4.4 and 4.5).

4.8 Undesirable effects

Summary of the safety profile
In clinical studies, sedation, vertigo, dizziness and nausea were observed as very common adverse reactions.

Table 1 of adverse reactions summarizes:

- Adverse reactions reported during clinical studies. All adverse reactions are listed according to frequency: 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
- The most commonly reported post-marketing adverse reactions. The side effects that occur in at least 1% of reports from health professionals and are considered expected are included. Frequency of events not reported in pivotal studies cannot be estimated and is given as not known.

Table 1: Adverse reactions reported in clinical studies						
System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1 000, <1/100)**	**Rare (≥1/10 000, <1/1,000)**	**Very rare (<1/10 000)**	**Not known (cannot be estimated from the available data)**
Immune system disorders				Hypersensitivity reactions	Anaphylactic shock	
Metabolism and nutrition disorders				Decreased appetite		

Table 1: <u>Adverse reactions reported in clinical studies</u>						
Psychiatric disorders			Confusion Euphoric mood Nervousness Depression Psychotic disorder Hallucination Depersonalisation	Depressed mood Agitation		
Nervous system disorders	Sedation Dizziness	Headache	Dysarthria Paraesthesia Coma Tremor	Seizures Abnormal coordination		
Eye disorders		Miosis	Blurred vision Diplopia Visual impairment Conjunctivitis			
Ear and labyrinth disorders	Vertigo		Tinnitus			
Cardiac disorders			Tachycardia Bradycardia Cyanosis Atrioventricular block second degree			
Vascular disorders		Orthostatic hypotension	Hypertension Pallor			
Respiratory, thoracic and mediastinal disorders		Hypoventilation	Dyspnoea (respiratory distress) Apnoea (respiratory arrest)		Bronchospasm	
Gastrointestinal disorders	Nausea	Vomiting	Loss of appetite Constipation Dyspepsia Flatulence	Diarrhoea		Dental caries
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritus Skin rash	Urticaria	Angioneurotic oedema (Quincke's oedema)	
Renal and urinary disorders			Urinary retention			
General disorders and administration site conditions			Asthenia Exhaustion Malaise			

<u>Drug dependence</u>

Repeated use of <INVENTED NAME> 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).

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 national reporting system listed in Appendix V.*

4.9 Overdose

Buprenorphine has a high safety index due to its partial opioid agonist/antagonist properties. However, particularly in non-tolerant individuals (especially children), serious poisoning (intoxication) may be induced by therapeutic doses. Even though the antagonist activity of buprenorphine may manifest at doses slightly above the recommended therapeutic range, doses in the recommended therapeutic range could, under certain circumstances, cause clinically significant respiratory depression (see section 4.4).

Symptoms

Symptoms of an excessive buprenorphine effect are characterised by symptoms such as “feeling strange”, poor concentration skills, sleepiness and possibly orthostatic dizziness. Manifestations of an acute overdose include miosis, sedation, hypotension, respiratory depression (reduction in breathing rate and/or respiratory volume, Cheyne-Stokes respiration, cyanosis), extreme sleepiness, impaired consciousness and even coma, skeletal muscle flaccidity, clammy skin and bradycardia. Nausea and vomiting may occur. The main symptom requiring intervention is respiratory depression, which might lead to respiratory arrest and death.

Treatment

In the event of an overdose, the patient’s cardiorespiratory status must be closely monitored and appropriate supportive measures must be instituted: Following standard intensive care, the symptoms of respiratory depression must be treated. Airway patency and supportive or controlled artificial ventilation must be ensured. In the event of vomiting, care must be taken to prevent aspiration of the vomitus. The patient should be transferred to a facility with complete resuscitation equipment. Use of an opioid antagonist, i.e. naloxone, is recommended despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine, compared with its effects on full agonist opioid agents. Naloxone might not be effective in reversing the respiratory depression induced by buprenorphine. The primary treatment of overdose should therefore be to restore adequate breathing activity, if necessary with mechanical support. When establishing the duration of treatment and medical surveillance required to reverse the effects of an overdose, the long duration of action of buprenorphine must be taken into account. Naloxone may be excreted more rapidly than buprenorphine, which may lead to recurrence of previously controlled symptoms of buprenorphine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: potent analgesic, partial opioid receptor agonist, ATC code: N02AE01

Mechanism of action
Buprenorphine is a potent, centrally acting analgesic with opioid agonist and antagonist properties (partial μ-opioid receptor agonist, κ-antagonist). The analgesic effect is based on interaction with specific opioid receptors (mainly μ-receptors) in the central nervous system.

Pharmacodynamic effects

The analgesic effect sets in after about 30 minutes. 0.4 mg buprenorphine administered sublingually has an analgesic effect equivalent to approximately 10 mg intramuscularly administered morphine. The

long duration of action of 6-8 hours can be explained by the slow dissociation of buprenorphine from the receptor and by the limited ability of morphine antagonists to abolish the effect, due to the high affinity of buprenorphine to the receptor.

In therapeutic doses, buprenorphine has respiratory depressing properties comparable to morphine in equianalgesic doses. Buprenorphine is potentiated by other agents with central depressant effects such as hypnotics, sedatives and alcohol.

Animal and human studies suggest that buprenorphine has a lower addictive effect than morphine.

5.2 Pharmacokinetic properties

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

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

Biotransformation
Buprenorphine is metabolised by 14-N-dealkulation and glucoroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirms that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N-desalkyl-buprenorphine is a μ (mu)- opioid agonist with weak intrinsic activity. Norbuprenorphine contributes to the overall pharmacological effect; however it is unknown to what extent.

Elimination
Elimination of buprenorphine is bi- or tri- exponential, with a long terminal elimination phase of 32 hours. This is in part due to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part due to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70 %). The residual 30 % is eliminated in the urine.

Special populations:
Elderly: No pharmacokinetic data in elderly patients available.

Renal impairment: Renal elimination plays a relatively small role (~ 30%) in the overall clearance of buprenorphine. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment.

Hepatic impairment: Hepatic elimination plays a relatively large role (~ 70%) in the overall clearance of buprenorphine and the action of buprenorphine may be prolonged in subjects with impaired hepatic clearance. Lower initial buprenorphine doses and cautious titration of dosage may be required in patients with mild to moderate hepatic dysfunction. Buprenorphine is contraindicated in patients with severe hepatic dysfunction (see section 4.3).

5.3 Preclinical safety data

In rats, there were found to be no undesirable effects on fertility or general reproductive performance. Investigations on rats and rabbits showed indications of fetotoxicity and post-implantation loss.

Studies in rats showed reduced intrauterine growth, delays in the development of some neurological

functions and high peri- and postnatal mortality among neonates after treatment of the dams during gestation or lactation. There are indications that difficult parturition and reduced milk production contributed to these effects. Signs of embryotoxicity including teratogenicity were absent in both rats and rabbits.

In vitro and *in vivo* studies to investigate the mutagenic potential of buprenorphine showed no clinically relevant effects.

Long-term studies on rats and mice did not indicate any carcinogenic potential of relevance to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol (E421)
Maize starch
Povidone K30 (E1201)
Citric acid monohydrate (E330)
Sodium citrate dihydrate (E331(iii))
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The sublingual tablets are packed in blisters consisting of Aluminium (base foil) laminated with aluminium sheets with 7, 10, 20, 28, 30, 50, 60, 70, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [to be completed nationally]

10. DATE OF REVISION OF THE TEXT

2026-09-16
[to be completed nationally]