SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buprenorphine G.L. Pharma 400 microgram sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 400 microgram buprenorphine (equivalent to 432 microgram buprenorphine hydrochloride).

Excipient with known effect: One tablet contains 29.628 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet

Buprenorphine G.L. Pharma 400 microgram sublingual tablets are white to off-white, round, biconvex tablets, with a diameter of approximately 5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As a strong analgesic for the relief of moderate to severe pain.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with buprenorphine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

Adults and children over 12

200-400 micrograms to be dissolved under the tongue every 6-8 hours or as required. The recommended starting dose for moderate to severe pain of the type typically presenting in general practice is 200 to 400 micrograms, 8 hourly.

Elderly

There is no evidence that dosage needs to be modified for the elderly.

Children under 12 years

Buprenorphine G.L. Pharma is suitable for use in children under 12 as follows:

16-25 kg (35-55 lb):	100 micrograms
25-37.5 kg (55-82.5 lb):	100-200 micrograms
37.5-50 kg (82.5-110 lb):	200-300 micrograms

The recommended dose should be administered every 6-8 hours.

Sublingual administration is not suitable for children under the age of six years.

Buprenorphine G.L. Pharma may be used in balanced anaesthetic techniques at a dose of 400 micrograms.

Special populations

Patients with hepatic insufficiency

Buprenorphine is metabolised in the liver. The degree and duration of its action may be different in patients with hepatic impairment. Therefore, the Buprenorphine G.L. Pharma dose should be reduced for these patients accordingly (see sections 4.4 and 5.2).

Method of administration

Sublingual use.

The tablet should not be chewed or swallowed whole as this will reduce efficacy.

Treatment goals and discontinuation

Before initiating treatment with Buprenorphine G.L. Pharma, 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 Buprenorphine G.L. Pharma, 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 treatment

Buprenorphine G.L. Pharma should not be used longer than necessary.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to other opiates.

4.4 Special warnings and precautions for use

Buprenorphine G.L. Pharma occasionally causes significant respiratory depression and, as with other strong centrally acting analgesics, care should be taken when treating patients with impaired respiratory function or patients who are receiving drugs which can cause respiratory depression. Although volunteer studies have indicated that opiate antagonists may not fully reverse the effects of Buprenorphine G.L. Pharma, clinical experience has shown that Naloxone may be of benefit in reversing a reduced respiratory rate. Respiratory stimulants such as Doxapram are also effective. The intensity and duration of action may be affected in patients with impaired liver failure.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

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

Seizures

Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder.

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 Buprenorphine G.L. Pharma. Repeated use of Buprenorphine G.L. Pharma 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 Buprenorphine G.L. Pharma 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 Buprenorphine G.L. Pharma 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 behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psychoactive drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced.

Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with buprenorphine.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Diversion

Diversion of Buprenorphine G.L. Pharma 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.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain.

This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Hepatic impairment

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study in which a buprenorphine/naloxone 2 mg/0.5 mg sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Since buprenorphine is extensively metabolised in the liver, plasma levels were found to be elevated for buprenorphine in patients with moderate and severe hepatic impairment, which may require dose adjustments.

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 to severe hepatic impairment (see section 5.2).

Athletes must be aware that this medicine may cause a positive reaction to ‘antidoping’ tests.

Excipients

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

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Buprenorphine G.L. Pharma should be used cautiously when co-administered with 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).

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.

There is evidence to indicate that therapeutic doses of buprenorphine do not reduce the analgesic efficacy of standard doses of an opioid agonist and that when buprenorphine is employed within the normal therapeutic range, standard doses of opioid agonist may be administered before the effects of the former have ended without compromising analgesia. However, in individuals on high doses of opioids

buprenorphine may precipitate abstinence effects due to its properties as a partial agonist.

Buprenorphine G.L. Pharma may cause some drowsiness which may be potentiated by other centrally acting agents, including alcohol, tranquillisers, sedatives and hypnotics.

Risk from concomitant use of sedatives such as benzodiazepines or related medicinal products:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use of sedative medicines should be limited (see section 4.4). The concomitant use of Buprenorphine G.L. Pharma with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Although interaction studies have not been performed, since the drug is metabolised by CYP3A4 (see section 5.2 pharmacokinetic properties), it is expected that gestodene, troleandomycin, ketoconazole, norfluoxetine, ritonavir, indinavir and saquinavir inhibit its metabolism. Alternatively, inducers of this enzyme such as phenobarbital, carbamazepine, phenytoin and rifampicin may reduce the levels of the drug. Since the magnitude of an inducing or inhibitory effect is unknown, such drug combinations should be avoided.

Buprenorphine G.L. Pharma has no known effects on diagnostic laboratory tests.

4.6 Fertility, pregnancy and lactation

Pregnancy

Buprenorphine G.L. Pharma is not recommended for use during pregnancy.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as buprenorphine may be secreted in breast milk and may cause respiratory depression in the infant. There is indirect evidence in animal studies to suggest that Buprenorphine G.L. Pharma may cause a reduction in milk flow during lactation. Although this occurred only at doses well in excess of the human dose, it should be borne in mind when treating lactating women.

4.7 Effects on ability to drive and use machines

If you feel drowsy after taking these tablets do not 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:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

Details regarding the new driving offence concerning driving after drugs have been taken in Great Britain may be found here: https://www.gov.uk/drug-driving-law

4.8 Undesirable effects

Nausea, vomiting, dizziness, sweating and drowsiness have been reported and may be more frequent in ambulant patients. Hallucinations and other psychotomimetic effects have occurred although more rarely than with other agonists/antagonists. Elderly patients would be expected to be more susceptible to these effects. Hypotension leading to syncope may occur. Rashes, headache, urinary retention and blurring of vision have occasionally been reported. Rarely, a serious allergic reaction may occur following a single dose. Buprenorphine G.L. Pharma occasionally causes significant respiratory depression (see section 4.4). Cases of dental caries have been reported with frequency not known (cannot be estimated from the available data).

Drug dependence (see section 4.4) and seizures have been reported with frequency not known (cannot be estimated from the available data). Drug withdrawal syndrome has been reported with frequency uncommon (≥1/1,000 to <1/100).

Drug dependence

Repeated use of Buprenorphine G.L. Pharma 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).

Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have also been reported.

During use of buprenorphine as substitution treatment the following adverse reactions have also been observed: hepatic necrosis and hepatitis.

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

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

The expected symptoms of overdose would be drowsiness, nausea and vomiting; marked miosis may occur.

Supportive measures should be instituted and if appropriate Naloxone or respiratory stimulants can be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Buprenorphine is a μ (mu) opioid partial agonist and κ (kappa) antagonist. It is a strong analgesic of the partial agonist (mixed agonist/antagonist) class.

5.2 Pharmacokinetic properties

Absorption

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

Peak plasma concentrations are achieved 90 minutes after sublingual administration.

Distribution

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

Biotransformation and elimination

Buprenorphine is oxidatively metabolised by 14-N-dealkylation to N-desalkylbuprenorphine (also known as norbuprenorphine) via cytochrome P450

CYP3A4 and by glucuroconjungation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is μ (mu) agonist with weak intrinsic activity.

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

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

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol
Maize starch
Povidone K30
Citric acid monohydrate
Sodium citrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The sublingual tablets are packed in blisters consisting of Aluminium (base foil) laminated with aluminium sheets with 7, 50, 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

G.L. Pharma GmbH
Schlossplatz 1
8502 Lannach
Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 21597/0117

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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