Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Temgesic 200 microgram Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect: Lactose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sublingual tablet.
White to creamy white circular biconvex sublingual tablet engraved with the letter 'L'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As a strong analgesic for the relief of moderate to severe pain such as occurs after surgery, with myocardial infarction or in patients with terminal or intractable disease.

4.2 Posology and method of administration

Posology
Adults and children over 12 weighing over 50 kg
1-2 tablets (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 1 to 2 tablets, 8 hourly.

Children over 37.5 kg:
Children weighing more than 37.5 kg and who are able to use a sublingual tablet, treatment can be started with one Temgesic 200 microgram sublingual tablets. The dose can be repeated every 6 to 8 hours.
The tablets should lie under the tongue until dissolved, which occurs in 5 to 10 minutes. They should not be chewed or swallowed. The dose may be repeated every 6-8. hours. Temgesic 400 microgram sublingual tablets should not be used in children.

Temgesic sublingual tablets should be not used for children weighing less than 37.5 kg.

Fixed intervals or daily doses should not be prescribed until an appropriate dosing interval is determined by clinical observation of the child.

Special populations

Hepatic impairment
As buprenorphine pharmacokinetics may be altered in patients with hepatic impairment, lower initial doses and careful dose titration in patients with hepatic impairment may be required (See section 4.4). *Buprenorphine should be used with caution in patients with hepatic insufficiency (see section 5.2).*

Renal Impairment
Modification of the buprenorphine dose is not generally required for patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (CLcr < 30 ml/min), which may require dose adjustment (See section 5.2).

Method of administration
The sublingual tablet should be kept under the tongue until it is dissolved, which happens within 5 to 10 minutes. They must not be chewed or swallowed.

4.3 Contraindications

Hypersensitivity to buprenorphine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 dosage.

Respiratory Depression
Clinically significant respiratory depression may occur within the recommended dose range in patients receiving therapeutic doses of Temgesic Care should be taken when treating 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 if Temgesic is administered to patients taking or recentlyreceiving drugs with CNS/respiratory depressant effects. Although volunteer studies have indicated that opiate antagonists may not fully reverse the effects of Temgesic, clinical experience has shown that naloxone may be of benefit in reversing a reduced respiratory rate. Respiratory stimulants such as doxapram are also effective.

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products
Concomitant use of Temgesic 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 Temgesic concomitantly with sedative medicinal products, 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).

Diversion
Diversion of Temgesic 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 of 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.

Dependence
Buprenorphine is a partial agonist at the μ (mu)-opioid receptor and chronic administration produces dependence of the opioid type. Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics.

Following chronic use, abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

In susceptible patients, dependence may lead to self-administration of the drug when pain no longer exists. Patients must not exceed the dosage of Temgesic prescribed by their physician, and patients should be urged to consult their physician if other prescription medications are currently being used or are prescribed for future use.

Use in opioid-dependent patients
Analgesic buprenorphine products may induce withdrawal symptoms in opioid dependent patients receiving full opioid agonists such as methadone or heroin.

Likewise, caution should be used when prescribing buprenorphine as an analgesic to individuals who are known to be drug abusers or patients with a history of opioid dependence. The current opioid dependence level of patients with a history of opioid abuse or misuse should be assessed prior to treatment with analgesic buprenorphine products.

Hepatic dysfunction
The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study. Since buprenorphine is extensively metabolized in the liver, plasma levels were found to be elevated for buprenorphine 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 to severe hepatic impairment.

Serotonin syndrome
Concomitant administration of Temgesic 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.

Use in ambulatory patients
Buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned accordingly.

Cardiovascular effects
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
Buprenorphine, like other potent opioids, may itself elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

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

Renal disease
Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine; therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} <30 ml/min).

Other opioid class warnings
Buprenorphine should be administered with caution in patients with the following conditions:
- elderly or debilitated
- myxoedema or hypothyroidism
- adrenal cortical insufficiency (e.g., Addison's disease)
- CNS depression or coma
- toxic psychoses
- prostatic hypertrophy or urethral stricture
- acute alcoholism
- delirium tremens
- kyphoscoliosis.

Monoamine oxidase inhibitors (MAOIs)
Caution should be exercised when Temgesic is used in combination with MAOI. (See section 4.5 Interaction with other medicinal products and other forms of interaction.)

Patients with lactose intolerance
This product contains lactose (see section 6.1). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Athletes must be aware that this medicine may cause a positive reaction to 'anti-doping' tests.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines 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 of sedative medicinal products should be limited and this combination must especially be avoided in cases where there is a risk of misuse. Patients must use benzodiazepines or related medicinal products concurrently with this product only as prescribed (see section 4.4).

Other central nervous system depressants
Patients receiving buprenorphine in the presence of other opioid derivatives (e.g. methadone, analgesics, general anaesthetics, phenothiazines, benzodiazepines, other tranquillisers, sedative-hypnotics, antitussives or antihistamines), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances (including alcohol) may increase CNS depression. When such combined therapy is contemplated, it is particularly important that the dose of one or both agents be reduced.

Alcohol
Buprenorphine should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine (see also section 4.7).

Naltrexone
The opioid antagonist, naltrexone, may antagonize the pharmacologic effect of buprenorphine. Patients treated with naltrexone may not receive the intended analgesic effectsof buprenorphine. Patients who have developed physical dependence to the effects of buprenorphine may experience a sudden onset of opioid withdrawal effects.

Other opioid analgesics
The analgesic effects of full agonist opioids may be competitively diminished by the partial agonist buprenorphine.
For patients who have developed a physiological dependence to full opioid agonists, administration of the partial agonist buprenorphine may elicit withdrawal symptoms (See also "Use in opioid dependent patients" under Section 4.4.).

CYP3A4 inhibitors
Since this drug is metabolised by the CYP3A4 isoenzyme *c*oadministration of drugs that *inhibit* CYP3A4 activity may cause decreased clearance of buprenorphine. Thus patients receiving buprenorphine co-administered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), or protease inhibitors (e.g., ritonavir) should be carefully monitored. Caution is advised when administering buprenorphine to patients receiving these medications, and if necessary, dose adjustments should be considered.

CYP3A4 inducers
Cytochrome P450 inducers, such as phenobarbital, carbamazepine, phenytoin and rifampicin, induce metabolism and may cause increased clearance of buprenorphine. Caution is advised when administering buprenorphine to patients receiving these medications, and if necessary, dose adjustments should be considered.

Monoamine oxidase inhibitors (MAOIs)
Based on experience with morphine, the concomitant use of MAOIs with buprenorphine might theoretically produce exaggeration of the effects of opioids and Temgesic should be used with caution in patients receiving monoamine oxidase inhibitors.

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

Other
Halothane is known to decrease hepatic clearance. Since hepatic elimination plays a relatively large role (~70%) in the overall clearance of buprenorphine, lower initial doses and cautious titration of dosage may be required when used with halothane.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Low dose buprenorphine products should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

At the end of pregnancy, high doses, even for a short duration of time, may induce respiratory depression in the newborn.

During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates.

Breastfeeding
Because buprenorphine and its metabolites pass into the mother's milk, buprenorphine should not be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

Low dose buprenorphine may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants. Ambulant patients should be warned not to drive or operate machinery until they are certain they can tolerate Temgesic.

4.8 Undesirable effects

4.8.1 Clinical Trial Data

Summary of the safety profile
Very common adverse reactions reported in clinical studies were sedation, vertigo, dizziness and nausea.

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

Tabulated list of adverse reactions

Table 1 lists adverse drug reactions reported in clinical studies. The frequency of possible side effects listed below is defined using the following convention:
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 (events not reported in registration trials cannot be estimated from the available post-marketing spontaneous reports).

Table 1. Adverse Drug Reactions Reported in Clinical Studies

Table 1. Adverse Drug Reactions Reported in Clinical Studies				
System Organ Class	***Very Common*** (≥1/10)	***Common*** (≥1/100 to <1/10)	***Uncommon*** (≥1/1000 to ≤1/100)	***Rare*** (≥1/10,000 to <1/1,000)
Immune system disorders				Hypersensitivity
Metabolism and nutrition disorders		`		Decreased appetite
Psychiatric disorders			Confusional state Euphoric mood Nervousness Depression Psychotic disorder Hallucination Depersonalisation	Dysphoria Agitation
Nervous system Disorders	Sedation Dizziness	Headache	Dysarthria Paraesthesia Coma Tremor	Convulsion Coordination abnormal
Eye disorders		Miosis	Vision blurred Diplopia Visual impairment Conjunctivitis	
Ear and labyrinth disorders	Vertigo		Tinnitus	
Cardiac disorders			Tachycardia Bradycardia Cyanosis Atrioventricular block second degree	
Vascular disorders		Hypotension	Hypertension Pallor	
Respiratory, thoracic and mediastinal disorders		Hypoventilation	Dyspnoea Apnoea	
Gastrointestinal disorders	Nausea	Vomiting	Dry mouth Constipation Dyspepsia Flatulence	Diarrhoea
Skin and subcutaneous tissue disorders		Hyperhidrosis	Pruritus Rash	Urticaria
Renal and urinary disorders			Urinary retention	
General disorders and administration site conditions			Asthenia Fatigue Malaise	

4.8.2 Post-marketing Data

Tabulated list of adverse reactions
The following is a list of the most commonly reported adverse drug reactions reported during post-marketing surveillance. Events occurring in at least 1% of reports by healthcare professionals, and considered expected are included. Serious reactions of anaphylactic shock, bronchospasm, and angioneurotic oedema have occurred at unknown rates, and are also included in Table 2. These adverse drug reactions are presented by MedDRA System, Organ, Class in internationally agreed order by preferred term and frequency of reporting.

Table 2: Spontaneous Adverse Drug Reactions Reported by Body System

Table 2: Spontaneous Adverse Drug Reactions Reported by Body System	
MedDRA System Organ Class	***Preferred Term***
Immune system disorders	Anaphylactic shock*
Psychiatric disorders	Confusional state Drug dependence Hallucination
Nervous system disorders	Somnolence Dizziness Headache
Vascular disorders	Hypotension
Respiratory thoracic and mediastinal disorders	Respiratory depression Bronchospasm*
Gastrointestinal disorders	Nausea Vomiting
Skin and subcutaneous tissue disorders	Pruritus Rash Hyperhidrosis Angioneurotic oedema*
General disorders and administration site conditions	Drug ineffective Drug interaction Fatigue

* frequency of reporting is less than 1% of postmarketing reports, but these items are included in Table 2 based upon seriousness of occurrence.

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:

HPRA Pharmacovigilance
Earlsfort Terrace, IRL - Dublin 2
Tel: +353 1 676497, Fax: +353 1 6762517
Website: www.hpra.ie, e-mail: medsafety@hpra.ie

4.9 Overdose

Overdose
Although the antagonist activity of buprenorphine may become manifest at doses somewhat above the recommended therapeutic range, doses in the recommended therapeutic range may produce clinically significant respiratory depression in certain circumstances (See Section 4.4 “Special Warnings and Precautions for Use”).

Symptoms
Manifestations of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed.
The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death.

Treatment
In the event of overdose, general supportive measures should be instituted including close monitoring of respiratory and cardiac status of the patient.

Symptomatic treatment of respiratory depression, following standard intensive care measures, should be performed. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment where full resuscitation facilities are available.

If the patient vomits, care must be taken to prevent aspiration of the vomitus.

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 to its effects on full agonist opioid agents.

Naloxone may not be effective in reversing the respiratory depression produced by buprenorphine; therefore, the primary management of overdose should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required.

The long duration of action of buprenorphine should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.

Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N02AE Oripavine derivatives and N02AE01 buprenorphine

Mechanism of action
Buprenorphine is a strong analgesic of the partial agonist (mixed agonist/antagonist) class.

5.2 Pharmacokinetic properties

Absorption
The drug is readily absorbed through buccal mucosa achieving therapeutic levels within 1 hour and maintaining an analgesic effect for 6-8 hours.

Biotransformation and elimination
This route reduces first pass metabolism in gut wall to some extent but extensive enterobiliary circulation of buprenorphine and its main metabolite occurs as with parenteral administration.

The major route of excretion is the intestine and faeces.

Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a postmarketing study.

Table 3 summarizes the results from a clinical trial in which the exposure of buprenorphine and naloxone was determined after administering a buprenorphine/naloxone 2.0/0.5mg sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 3. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following buprenorphine/naloxone administration (change relative to healthy subjects)

PK Parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
Buprenorphine			
C_{max}	1.2-fold increase	1.1-fold Increase	1.7-fold increase
AUC_{last}	Similar to control	1.6-fold increase	2.8-fold increase

Overall, buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function.

5.3 Preclinical safety data

The overall conclusion from all pharmacology and toxicology studies was that there is nothing to suggest that buprenorphine will be toxic to humans at doses far in excess of the therapeutic dosage level.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 year - PVC/PVDC aluminium blister strip
3 years - Nylon/aluminium/uPVC blister strip
3 years - HDPE bottle

6.4 Special precautions for storage

- PVC/PVDC aluminium blister: Do not store above 25°C. Store in the original package.
- Nylon/aluminium/uPVC blister: Do not store above 30°C. Store in the original package.
- HDPE bottle: Do not store above 30°C

6.5 Nature and contents of container

- PVC/PVDC aluminium foil blister strips of 10 tablets each, packed in cartons of 50 tablets.
- Nylon/aluminium/uPVC blister strips of 10 tablets each, packed in cartons of 50 tablets.
- HDPE bottle with dessicant and child-resistant closure, containing 50 tablets.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Eumedica Pharmaceuticals GmbH
Basler Straße 126
Lörrach
79540
Germany

8 MARKETING AUTHORISATION NUMBER

PA23460/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 30 March 2007

10 DATE OF REVISION OF THE TEXT

April 2023