

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Temgesic 300 micrograms/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains buprenorphine 300 micrograms (as hydrochloride).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless sterile solution for injection.

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

Posology

Adults and children over 12 years: 1-2ml (300-600 micrograms of buprenorphine) every 6-8 hours or as required.

Children aged under 12 years: 3-6 micrograms/kg body weight every 6-8 hours. In refractory cases up to 9 micrograms/kg may be administered.

There is no clinical experience in infants below the age of 6 months.

There is no evidence that dosage need be modified for the elderly. However, elderly patients are likely to be more susceptible to the adverse effects of Temgesic (see Section 4.8).

Temgesic Injection may be employed in balanced anaesthetic techniques as a pre-medication at a dose of 300 micrograms i.m., or as an analgesic supplement at doses of 300-450 micrograms i.v.

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).

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 (CL_{cr} < 30 ml/min), which may require dose adjustment (See section 5.2).

Method of administration

Administration by i.m. or slow i.v. injection.

Treatment goals and discontinuation

Before initiating treatment with Temgesic, 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 Temgesic,

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

Temgesic should not be used longer than necessary.

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

As with other potent opioids, 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 recently receiving 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 medicines such as benzodiazepines or related drugs

Concomitant use of Temgesic 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 Temgesic concomitantly with sedative medicines, 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).

Diversion

Diversion of Temgesic has been reported. Diversion refers to the introduction of buprenorphine into the illicit market either by patients or individuals who obtain the medicinal product through theft from patients or pharmacies. The diversion may lead to new addicts using buprenorphine as the primary drug of abuse, with the risks of overdose, spread of blood borne viral infection and respiratory depression.

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 Temgesic. Buprenorphine is a partial agonist at the μ (μ)-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.

Repeated use of Temgesic 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 Temgesic 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 Temgesic 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.

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.)

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

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines such as benzodiazepines or related drugs

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 should be limited (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, sedatives/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. The concomitant use of Temgesic with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Benzodiazepines

A number of deaths and cases of coma have occurred when addicts have intravenously misused buprenorphine and benzodiazepines concomitantly.

There have been reports of respiratory and cardiovascular collapse in patients who received therapeutic doses of diazepam and analgesic doses of buprenorphine; therefore, dosages must be limited and this combination must especially be avoided in cases where there is a risk of misuse. Patients must use benzodiazepines concurrently with this product only as prescribed (see section 4.4).

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 effects of 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 the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, coadministration 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, rifampicin, carbamazepine, and phenytoin, 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). 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.

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

Fertility and 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.

Breast-feeding

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 commonly reported 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 ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (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 ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1000$ to $\leq 1/100$)	Rare ($> 1/10,000$ to $\leq 1/1,000$)
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	

Drug dependence

Repeated use of Temgesic 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).

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 6764971, 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

Distribution

Buprenorphine is readily available by i.v. or i.m. routes; the relative bioavailability i.m. to i.v. was 1.07. Peak plasma levels are achieved within a few minutes of i.m. administration and after 10 minutes are not significantly different from those observed after the same dose given i.v.

5.3 Preclinical safety data

No preclinical findings of relevance to the prescriber have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose (dextrose) monohydrate

Hydrochloric acid, concentrated (for pH adjustment)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 3 years.

Once opened, solution should be used immediately.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package to protect from light

Once opened, any unused solution should be discarded.

6.5 Nature and contents of container

Sealed Type I glass ampoule containing 1 ml of solution.

Pack size: five ampoules in a cardboard carton.

6.6 Special precautions for disposal

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

PA23460/001/002

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Date of last renewal: 30 March 2007

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