NAME OF THE DRUG
TEMGESIC INJECTION and TEMGESIC SUBLINGUAL TABLETS.

Active Ingredient: Buprenorphine hydrochloride

DESCRIPTION
TEMGESIC is a synthetic opioid agonist-antagonistic analgesic. It is available in two dosage forms containing the active ingredient buprenorphine hydrochloride.

Each 1mL of TEMGESIC Injection contains 324µg buprenorphine hydrochloride (equivalent to 300µg buprenorphine), 50mg glucose anhydrous, water for injections and hydrochloric acid to adjust the pH to approximately 4.0.

Each TEMGESIC Sublingual Tablet contains 216µg buprenorphine hydrochloride (equivalent to 200µg buprenorphine). Each tablet also contains lactose, mannitol, maize starch, povidone, magnesium stearate, citric acid - anhydrous and sodium citrate.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg/mL at 37°C, pH 4.1). Chemically, buprenorphine is 21-Cyclopropyl-7α-[((S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine hydrochloride. Buprenorphine hydrochloride has the molecular formula C_{29} H_{41} NO_4 HCl and the molecular weight is 504.09. The CAS number is 53152-21-9. The chemical structure of buprenorphine is:

![Chemical structure of buprenorphine](image)

PHARMACOLOGY
Site and mode of action
Buprenorphine is a partial agonist with high affinity for the morphine receptor, demonstrating both agonist and antagonist properties. The drug receptor complex is very stable and dissociates slowly.

Pharmacodynamics
In a number of standard animal antinociceptive tests, buprenorphine displays potent analgesic activity, often with a curvilinear or bell-shaped dose-response in which 'higher' doses produce a lesser effect than 'lower' doses.

In such tests, buprenorphine is more potent than other opiate analgesics, such as morphine (30x) and pentazocine (100x) and at equi-analgesic doses the duration of action of buprenorphine in these animal tests is at least 4x as long as morphine.

Buprenorphine does not substitute for morphine in dependent rats; rather, it precipitates signs of abstinence and is at least as potent as naloxone in antagonising morphine-induced analgesia in rodents.

In animal tests for physical dependence liability, buprenorphine has the least capability of any opioid
tested, being lower than codeine and pentazocine. In chronically-treated primates neither abrupt withdrawal nor administration of narcotic antagonists could precipitate abstinence. In view of the receptor kinetics of buprenorphine, this is not an unexpected result.

Although buprenorphine produces initial immobility in rodents followed by increased locomotor activity, higher doses in primates produce only mild signs of CNS depression.

Buprenorphine slightly decreases the respiratory rate in mice, cats and dogs. Arterial blood gas measurements in rats showed that buprenorphine, unlike morphine, has a bell-shaped dose-response curve in the dose range 0.01-30mg/kg intra-arterially, with a ceiling effect such that the maximum depression of respiration seen with buprenorphine was significantly less than that with morphine. In man, respiratory depression in the CO₂ response model increased linearly with doses up to 1.2mg, which was the highest tested. The peak depressant effect with buprenorphine occurred at 3-5 hours compared to 1-2 hours with morphine. However, doses up to 7mg i.v. (equivalent to 200mg morphine) have been given to patients without clinically significant respiratory effects.

Buprenorphine at high doses causes a slight reduction in heart rate in rats and dogs, but has little effect on arterial blood pressure. Major cardiovascular changes are unlikely to occur after therapeutic doses. At therapeutic doses, blood pressure and pulse rate may fall slightly, the maximum changes observed being 10-15%. A clinical trial of intravenous buprenorphine to treat chest pain associated with myocardial infarction showed no significant changes in systemic or pulmonary arterial blood pressure or in heart rate. During the period of reduced cardiac reserve after open heart surgery, intravenous buprenorphine effected no significant changes in cardiac output, mean arterial pressure or peripheral resistance.

Because of the stability of the complex formed between buprenorphine and the opiate receptor, antagonists are only partially effective in reversing the effect of established buprenorphine compared to the situation when the antagonist is administered prior to buprenorphine.

At very high doses there is evidence from animal studies for developing tolerance to buprenorphine and cross tolerance with morphine.

Animal studies have shown evidence for a potentiation of action between buprenorphine and centrally-acting drugs likely to be used concurrently, such as halothane, fluothane and thiopentone sodium.

**Pharmacokinetics**

Systemic availability of parenterally administered buprenorphine is generally close to 100%. Plasma levels in patients following an intravenous or intramuscular dose of 300µg are maximal at 2 minutes and 5 minutes, respectively. At 10 minutes the plasma concentration from intramuscular and intravenous doses are essentially identical. The buprenorphine plasma level data achieved after these doses most closely fit a tri-exponential decay curve, with a very fast initial distribution phase (t½ 2 minutes) and a slow elimination phase (t½ approximately 5 hours).

When buprenorphine is taken at much higher doses, for the treatment of opioid addiction, a long terminal elimination phase - half-life 34.6 hours is observed. This phase follows the elimination phase with the half-life of 5 hours and can not be measured following normal analgesic doses because plasma levels are too low to be measured. The 5 hour half-life should be considered the clinically relevant elimination rate for TEMGESIC.

Buprenorphine from TEMGESIC Sublingual Tablets has been formulated to allow the active ingredient to be absorbed through the sublingual mucosa within minutes and consequently, buprenorphine bypasses 'first pass' metabolism by the intestinal mucosa and the liver, which is known to be significant following oral administration. Peak concentrations of buprenorphine following sublingual administration are achieved within 2-4 hours. The absolute bioavailability of buprenorphine by the sublingual route is approximately 35%. Following sublingual buprenorphine, the terminal half-life was not significantly different from that calculated following the parenteral route.
The clinical efficacy observed for buprenorphine administered by both the parenteral and sublingual routes in conjunction with the different pharmacokinetic profile indicates that there is no obvious correlation between plasma level and clinical effect. At therapeutic doses the drug is highly protein bound (approximately 96%) primarily to alpha and beta-globulin fractions.

After intramuscular administration of \( [^3\text{H}] \)-buprenorphine to one volunteer, 68% of the radioactivity was recovered in the faeces and 27% in the urine. Metabolism of buprenorphine administered either parenterally or sublingually is predominantly in the liver, with the principal metabolites being the N-dealkylated product and its glucuronide, together with glucuronides of the parent drug. Excretion is predominantly by the biliary route with some evidence for enterohepatic cycling following intestinal deconjugation.

**INDICATIOnS**
Strong analgesic for the short-term (not more than one week) relief of moderate to severe pain, including post-operative and terminal pain. TEMGESIC Injection should be employed when sublingual administration is not practical e.g. pre- or peri-operatively. It is not recommended for use in children.

TEMGESIC does not have an approved role in opioid dependence rehabilitation programs.

**CONTRAINDICATIONS**
Pregnancy and Lactation (see Use in Pregnancy and Use in Lactation).

TEMGESIC should not be administered to patients who have been shown to be hypersensitive to buprenorphine or other opiates. Hypersensitivity to any of the ingredients.

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

**Use in Opiate Dependent Patients**
Because of the narcotic antagonist activity of buprenorphine, use in individuals dependent on other opioids may result in withdrawal effects.

**Cardiovascular Effects**
Buprenorphine may cause a slight reduction in pulse rate and blood pressure in some patients.

**Respiratory Depression**
TEMGESIC occasionally causes significant respiratory depression and, as with other strong centrally acting analgesics, care should be taken when treating patients with impaired respiratory function (eg chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression) or patients who are receiving drugs which can cause respiratory depression.

Respiratory depression following sublingual buprenorphine is more likely to occur with doses exceeding 400\( \mu \text{g} \).

Should respiratory depression occur to a clinically undesirable degree, supportive measures should be used to maintain adequate ventilation and oxygenation. The effects of buprenorphine are only partially reversed by standard narcotic reversal agents, such as naloxone.

**Interaction with Other Central Nervous System Depressants**
Patients receiving TEMGESIC in the presence of other narcotic analgesics, general anaesthetics, antihistamines, benzodiazepines, phenothiazines, other tranquilisers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, it is particularly important that the dose of one or both agents be reduced.
Head Injury and Increased Intracranial Pressure
TEMGESIC, like other potent opiates 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. TEMGESIC can produce miosis and changes in the level of consciousness that may interfere with patient evaluation. The miosis is more marked than with morphine and persists for more than 24 hours.

Hepatic Dysfunction
Because buprenorphine is metabolised by the liver, the intensity and duration of its action may be altered in those individuals with impaired hepatic function. Since hepatic elimination plays a relatively large role (~70%) in the overall clearance of TEMGESIC, lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.

Renal Disease
Renal elimination plays a relatively small role (~30%) in the overall clearance of TEMGESIC. Therefore no dose modification based on renal function is required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min).

Buprenorphine increases intracholedochal pressure as do other opiates. Therefore, caution should be exercised when TEMGESIC is to be administered to patients with dysfunction of the biliary tract.

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

Use in Ambulatory Patients
TEMGESIC 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. Like other opiates, TEMGESIC may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy (Category C)
TEMGESIC is contraindicated in pregnant women (See CONTRAINDICATIONS). Buprenorphine readily crosses the placental barrier and may cause respiratory depression in neonates. The safety of buprenorphine in pregnancy has not been established and therefore, it should not be used in women who are pregnant or who are likely to become pregnant.

Treatment with buprenorphine during pregnancy was associated with difficult parturition and fetotoxicity, including post-implantation loss and decreased post-natal survival, in rats and rabbits at systemic exposures similar to the maximum anticipated human exposure of buprenorphine used for opiate addiction treatment (32 mg/day); this is 20 fold the recommended upper analgesic dose of 1.6mg/day. Evidence for teratology was not evident in animal studies.

Maternal oral administration at high doses (80mg/kg/day) during gestation and lactation resulted in a delayed postnatal development of some neurological functions (surface righting reflex and startle response) in neonatal rats with a NOEL of 8mg/kg/day PO (representing a six fold systemic exposure at the maximum anticipated clinical exposure for analgesia).

Use in Lactation
Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. Decreases in postnatal survival, growth and development were also observed in animals treated with buprenorphine during lactation. Because buprenorphine passes into the mother's milk, TEMGESIC should not be used in breast-feeding women.

Interactions with Other Drugs
A number of deaths and cases of coma have occurred when addicts have intravenously misused buprenorphine and benzodiazepines concomitantly. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines or other CNS depressants at the same time as receiving TEMGESIC.
CYP 3A4 Inhibitors
Buprenorphine is metabolized to norbuprenorphine by cytochrome P450 3A4. Caution is advised when buprenorphine is administered concomitantly with specific inhibitors of CYP 3A4 (e.g. protease inhibitors, some drugs in the drug classes of azole antimycotics, calcium channel antagonists, and macrolide antibiotics) as this may lead to increased levels of buprenorphine due to inhibition of the formation of norbuprenorphine. Whilst these interactions are more likely to be clinically significant at buprenorphine dose levels used for opiate addiction treatments, doses of buprenorphine should be carefully titrated in patients receiving concomitant administration of CYP 3A4 inhibitors.

CYP 3A4 Inducers
Cytochrome P450 inducers, such as rifampicin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of buprenorphine. Caution is advised when administering TEMGESIC to patients receiving these medications and if necessary dose adjustments should be considered.

Monoamine Oxidase Inhibitors
Until further information is available, buprenorphine should be used with caution in patients receiving monoamine oxidase inhibitors, as these may intensify its adverse effects.

CNS Depressants
Buprenorphine may cause some drowsiness and this could be potentiated by other narcotic analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquillisers, sedative/hypnotics or other CNS depressants (including alcohol). When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. Ambulant patients should be warned not to drive or operate machinery if affected (see Use in Ambulatory Patients under PRECAUTIONS).

Narcotic Antagonist Activity
Buprenorphine demonstrates narcotic antagonistic activity and has been shown to reverse the effects of peri-operatively administered narcotics. It may, therefore, precipitate withdrawal symptoms in narcotic addicts and it should be given with care, initially, to patients previously treated with narcotic analgesics.

Effects on Laboratory Tests
Athletes should be aware that this medicine may cause a positive reaction to “anti-doping” tests

ADVERSE REACTIONS

Drowsiness, or sleep from which the patient can easily be aroused, occurs in most patients, particularly in the post-operative period.

Other less frequent adverse reactions occurring in 5-10% of patients are:
Nausea
Dizziness/vertigo

Adverse reactions occurring in 1-5% of the patients are:
Sweating, Hypotension, Vomiting, Miosis, Headache, Nausea/vomiting, Hypoventilation

Adverse reactions occurring in less than 1% of patients are:
CNS Effect: Confusion, blurred vision, euphoria, weakness/fatigue, dry mouth, nervousness, depression, slurred speech, paresthesia.
Cardiovascular: hypertension, tachycardia, bradycardia
Gastrointestinal: Constipation
Respiratory: dyspnoea, cyanosis
Dermatological: pruritus
Ophthalmological: diplopia, visual abnormalities
Miscellaneous: injection site reaction, urinary retention, dreaming, flushing/warmth, chills/cold, tinnitus, conjunctivitis, Wenckebach block, and psychosis

Other adverse events observed infrequently include the following:
Malaise, hallucinations, depersonalisation, coma, dyspepsia, flatulence, apnoea, rash, amblyopia, tremor, and pallor.

The following reactions have been reported to occur rarely:
Loss of appetite, dysphoria/agitation, diarrhoea, urticaria, and convulsions/lack of muscle coordination.

Allergic reactions
Cases of acute and chronic hypersensitivity to buprenorphine have been reported. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic, oedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to TEMGESIC.

DEPENDENCE LIABILITY
Buprenorphine is a partial agonist of the morphine type i.e. it has certain opioid properties which may lead to psychological dependence of the morphine type due to an opioid-like euphoric component of the drug. Direct dependence studies have shown minor physical dependence on withdrawal of the drug. However, caution should be used when prescribing to individuals who are known to be drug abusers or ex-narcotic addicts. TEMGESIC may not substitute in acutely-dependent narcotic addicts due to its antagonist component.

DOSEAGE AND ADMINISTRATION
TEMGESIC Injection
The recommended dosage is 300-600 µg by intramuscular or slow intravenous injection, repeated every 6-8 hours, or as required.

TEMGESIC Sublingual Tablets
1 to 2 tablets (200-400 µg buprenorphine) to be dissolved under the tongue every 6-8 hours, or as required. Tablets should be kept in place for 10 minutes without swallowing. The tablets should not be chewed or swallowed as this will reduce their efficacy.

OVERDOSE
Symptoms
Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

In the event of accidental overdose, general supportive measures should be instituted including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment
In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

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.
PRESENTATION AND STORAGE CONDITIONS
TEMGESIC Injection contains 300µg/mL buprenorphine as the hydrochloride in a 5% glucose solution. It is a colourless liquid in clear glass snap-ampoules of 1mL in packs of 5.

TEMGESIC Sublingual Tablets contain 200µg buprenorphine as the hydrochloride. The tablets are white, circular, biconvex and engraved with a sword symbol on one side and “L” on the reverse side.

The tablets are packaged in:
- Aluminium/Aluminium blister packs of 10 tablets each in cartons containing 50 tablets. These packs must be stored below 30C and protected from light.

POISON SCHEDULE
Schedule 8 – Controlled Drug

NAME AND ADDRESS OF SPONSOR

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