AUSTRALIAN PRODUCT INFORMATION

TEMPGESIC® (BUPRENORPHINE)

1 NAME OF THE MEDICINE

TEMPGESIC INJECTION and TEMGESIC SUBLINGUAL TABLETS contain buprenorphine (as hydrochloride).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1mL of TEMGESIC Injection contains 300 micrograms of buprenorphine (as hydrochloride).

Each TEMGESIC Sublingual Tablet contains 200 micrograms of buprenorphine (as hydrochloride).

Excipients with known effect:
TEMPGESIC Injection contains glucose.
TEMPGESIC Sublingual Tablets contain lactose monohydrate and mannitol.

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.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg/mL at 37°C, pH 4.1).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

TEMPGESIC Injection – Colourless liquid in clear glass snap-ampoules.
TEMPGESIC Sublingual tablets - White, circular, biconvex tablets debossed with a "L".

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

TEMPGESIC does not have an approved role in opioid dependence rehabilitation programmes.

4.2 DOSE AND METHOD OF ADMINISTRATION

TEMPGESIC Injection
The ampoule should be inspected visually for particulate matter and discoloration prior to administration.

The recommended dosage is 300-600 micrograms by intramuscular or slow intravenous injection, repeated every 6-8 hours, or as required.

TEMPGESIC Sublingual Tablets
The sublingual formulation is not designed to be split or broken. The tablets should not be chewed or swallowed as this will reduce their efficacy. The usual recommended dose is 1 to 2 tablets 200-
400 micrograms of buprenorphine dissolved under the tongue every 6-8 hours, or as required. Tablets should be kept in place for 10 minutes without swallowing.

4.3 **CONTRAINDICATIONS**

Pregnancy and Lactation (see section 4.6 - 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 opioids. Hypersensitivity to any of the ingredients.

4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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.

**General**

TEMGESIC should be administered with caution in debilitated patients and those with myxoedema or hypothyroidism, adrenal cortical insufficiency (e.g. Addison's disease); toxic psychoses; orthostatic hypotension; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

**Psychological dependence (addiction), abuse, misuse and diversion**

Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics. In humans, limited euphoric effects have been observed with buprenorphine.

However, as with other opioids, there is a potential for abuse of the drug and for development of strong psychological dependence.

Although the risk of addiction in any individual is unknown, it may occur in patients appropriately prescribed TEMGESIC and in those who obtain the drug illicitly. Psychological and/or physical dependence may occur at recommended doses and if the drug is misused or abused. Assess each patient's risk for addiction to opioids, abuse, or misuse prior to prescribing TEMGESIC and monitor all patients receiving TEMGESIC for the development of these behaviours or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression).

The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids, but use in such patients necessitates comprehensive counselling about the risks and proper use of opioids, along with close monitoring for signs of addiction, abuse, or misuse.

TEMGESIC, like other opioids, can be diverted for non-medical use into illicit channels of distribution. TEMGESIC should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential. Abuse of opioids poses a risk of overdose and death. This risk is increased with concurrent abuse of opioids with alcohol and other substances including other opioids and benzodiazepines.

**Use in Opioid Dependent Patients**

Because of the narcotic antagonist activity of buprenorphine, use in individuals dependent on other opioids may result in withdrawal effects. 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.
Elderly
The safety and efficacy of buprenorphine in elderly patients over 65 years have not been established.

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.

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 (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression) or patients who are receiving drugs which can cause CNS and/or respiratory depression.

Respiratory depression following sublingual buprenorphine is more likely to occur with doses exceeding 400 micrograms.

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. Patients with the physical and/or pharmacological risk factors above should be monitored and dose reduction may be considered.

CNS Depression
Patients receiving buprenorphine in the presence of other opioid analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquilisers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. 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 section 4.7 Effects on Ability to Drive and Use Machines).

Head Injury and Increased Intracranial Pressure
TEMGESIC, 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. 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 Impairment
The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study. Plasma levels were found to be elevated for buprenorphine in patients with moderate to severe hepatic impairment. Since hepatic elimination plays a relatively large role (~70%) in the overall clearance of TEMGESIC, the intensity and duration of its action may be altered in those individuals with impaired hepatic function. Buprenorphine should be used with caution in patients with moderate to severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.

Buprenorphine increases intracholedochal pressure as do other opioids. Therefore, caution should be exercised when TEMGESIC is to be administered to patients with dysfunction of the biliary tract.
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 generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min).

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

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.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Alcohol
Buprenorphine should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine.

Other central nervous system depressants
Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. Examples of central nervous system depressants include: other opioid analgesics or antitussives, general anaesthetics, certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine and other CNS depressants. When such combined therapy is contemplated, it is particularly important that the dose of one or both agents be reduced.

Naltrexone and other opioid antagonists
Opioid antagonists such as 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 effect.

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 section 4.4 Special Warnings and Precautions for Use - Use in Opioid Dependent Patients.)
CYP 3A4 Inhibitors
Since the metabolism of buprenorphine to norbuprenorphine is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance and hence increased levels of buprenorphine. Thus patients receiving buprenorphine coadministered 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.

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.

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

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

Effects on fertility
There were no effects on mating performance or on fertility of male rats following short term treatment with buprenorphine.

Use in pregnancy (Category C)
TEMGESIC is contraindicated in pregnant women (See section 4.3 Contraindications).

There are no adequate and well-controlled studies in pregnant women.

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.

Buprenorphine readily crosses the placental barrier and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates.

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 opioid 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.

### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TEMGESIC may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. TEMGESIC can cause drowsiness, particularly when taken together with alcohol or central nervous system depressants. Patients should be cautioned accordingly.

### 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Very commonly reported adverse reactions reported in clinical studies were sedation, vertigo, dizziness and nausea.

**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: Treatment-related adverse reactions reported in clinical studies of buprenorphine (Temgesic) |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| **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 | Dysphoria |
| | Nervousness | Depression | Agitation |
| | Psychotic disorder | Psychotic disorder | |
| | Hallucination | Hallucination | |
| | Depersonalisation | Depersonalisation | |
| **Nervous system disorders** | Sedation | Headache | Convulsion |
| | Dizziness | | Coordination abnormal |
| | Drowsiness | | |
| | Sleep | | |
**Table 1: Treatment-related adverse reactions reported in clinical studies of buprenorphine (Temgesic)**

<table>
<thead>
<tr>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
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</thead>
<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
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<tr>
<td>Miosis</td>
<td>Vision blurred</td>
<td>Dioplia</td>
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<tr>
<td></td>
<td>Vision blurred</td>
<td>Diplopia</td>
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<tr>
<td></td>
<td>Vision blurred</td>
<td>Visual impairment</td>
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<tr>
<td></td>
<td>Vision blurred</td>
<td>Conjunctivitis</td>
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<tr>
<td></td>
<td>Vision blurred</td>
<td>Amblyopia</td>
<td></td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>Tinnitus</td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td>Tachycardia</td>
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<tr>
<td></td>
<td>Bradycardia</td>
<td>Cyanosis</td>
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<tr>
<td></td>
<td>Atrioventricular block second degree</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td>Hypotension</td>
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<tr>
<td></td>
<td>Hypertension</td>
<td>Pallor</td>
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<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
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<td></td>
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<tr>
<td>Hypoventilation</td>
<td>Dyspnoea</td>
<td>Apnoea</td>
<td></td>
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<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Vomiting</td>
<td>Dry mouth</td>
<td>Diarrhoea</td>
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<tr>
<td></td>
<td></td>
<td>Constipation</td>
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<tr>
<td></td>
<td></td>
<td>Dyspepsia</td>
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<tr>
<td></td>
<td></td>
<td>Flatulence</td>
<td></td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<tr>
<td>Hyperhidrosis</td>
<td>Pruritus</td>
<td>Rash</td>
<td>Urticaria</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Urinary retention</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Asthenia*</td>
<td>Fatigue</td>
<td>Malaise</td>
<td>Injection site reaction</td>
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<tr>
<td></td>
<td></td>
<td>Flushing/warmth</td>
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<td></td>
<td></td>
<td>Chills/cold</td>
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<td></td>
<td></td>
<td>Dreaming</td>
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</tbody>
</table>

**Post-marketing Data**

The following 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>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Anaphylactic shock</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Confusional state</td>
</tr>
<tr>
<td></td>
<td>Drug dependence</td>
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<tr>
<td></td>
<td>Hallucination</td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Somnolence</td>
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<tr>
<td></td>
<td>Dizziness</td>
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<tr>
<td></td>
<td>Headache</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td>Hypotension</td>
</tr>
<tr>
<td><strong>Respiratory thoracic and mediastinal disorders</strong></td>
<td>Respiratory depression</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
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<tr>
<td></td>
<td>Hyperhidrosis</td>
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<tr>
<td></td>
<td>Angioneurotic oedema</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Drug ineffective</td>
</tr>
<tr>
<td></td>
<td>Drug interaction</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

4.9 OVERDOSE

**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. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation following standard intensive care measures. The patient should be transferred to an environment within which full resuscitation facilities are available.

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

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. 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. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose. If naloxone is used 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, so a continuing infusion may be necessary. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

For further information on the management of overdose, contact the Poison Information Centre on 131 126 (Australia) or the National Poisons Centre on 0800 764 766 (New Zealand).
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Site and mode of action
Buprenorphine is a µ-opioid partial agonist with high affinity for the µ-opioid receptor, demonstrating both agonist and antagonist properties. The drug receptor complex is very stable and dissociates slowly. Buprenorphine is also an antagonist at the κ-opioid receptor.

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 opioid 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 opioid 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.

5.2 PHARMACOKINETIC PROPERTIES

Systemic availability of parenterally administered buprenorphine is generally close to 100%. Plasma levels in patients following an intravenous or intramuscular dose of 300 micrograms 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 cannot 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 by-passes '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 [3H]-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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There was no evidence of genotoxicity for buprenorphine in bacterial gene mutation assays, chromosomal aberration studies and a mouse lymphoma assay.

Carcinogenicity

No data available
6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TEMGESIC Injection:
Glucose 55 mg (equivalent to anhydrous glucose 50 mg), water for injections and hydrochloric acid (to pH 4.0).

TEMGESIC Sublingual Tablets:
Lactose monohydrate, mannitol, maize starch, povidone, magnesium stearate, citric acid and sodium citrate dihydrate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

TEMGESIC Injection and tablets in Al/Al blister pack and HDPE bottle: 3 years
TEMGESIC Sublingual Tablets in PVC/PVdC/Al blister pack: 9 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

TEMGESIC Injection and Sublingual Tablets in Al/Al blister pack and HDPE bottle: Store below 30°C. Protect from light.
TEMGESIC Sublingual Tablets in PVC/PVdC/Al blister pack: Store below 25°C and protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

TEMGESIC Injection: 1 mL clear glass snap-ampoules in packs of 5 (AUST R 15394).

TEMGESIC Sublingual Tablets
- Al/Al blister packs of 10 tablets each in cartons containing 50 tablets (AUST R: 34091; not marketed in New Zealand).
- PVC/PVdC/Al blister packs of 10 tablets each in cartons containing 50 tablets (AUST R: 34091; not marketed in Australia or New Zealand).
- HDPE bottles with child-resistant reclosable cap containing 50 tablets (AUST R: 150453; not marketed in Australia or New Zealand).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
The chemical structure of buprenorphine is:

![Chemical structure diagram]

CAS number
The CAS number is 53152-21-9.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 - Controlled Drug

8 SPONSOR

Indivior Pty Ltd
78 Waterloo Road
Macquarie Park NSW 2113
Australia

For adverse event reporting please contact:
Indivior Pty Ltd
+800-270-81901
PatientSafetyRoW@indivior.com

9 DATE OF FIRST APPROVAL

30th September 1991

10 DATE OF REVISION

22 January 2019
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