WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, TEMGESIC should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain *(*see section *4.4 Special Warnings and Precautions for Use).*

Hazardous and harmful use

TEMGESIC poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section *4.4. Special Warnings and Precautions for Use)*.

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of TEMGESIC. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase *(*see section *4.4 Special Warnings and Precautions for Use)*.

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking TEMGESIC.

1 PRODUCT NAME

TEMGESIC INJECTION 300 micrograms/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Buprenorphine (as hydrochloride) 300 micrograms/mL

Excipients with known effect: 55 mg glucose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. Colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TEMGESIC injection is indicated for the short-term (not more than one week) management of severe pain for which other treatment options have failed, are contraindicated, not tolerated or are otherwise inappropriate to provide sufficient management of pain.

TEMGESIC is not recommended for use in children.

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

4.2 Dose and method of administration

The ampoule should be inspected visually for particulate matter and discolouration prior to administration.

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

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 to 450 micrograms i.v.

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.

TEMGESIC is contraindicated for use in patients with severe respiratory disease, acute respiratory disease and respiratory depression.

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.

Hazardous and harmful use

TEMGESIC contains the opioid buprenorphine and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed TEMGESIC at recommended doses

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed TEMGESIC.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see section *6.4 Special precautions for storage* and section *6.6 Special precautions for disposal*). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share TEMGESIC with anyone else.

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 medicine 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 the Elderly

The safety and efficacy of buprenorphine in elderly patients over 65 years have not been established (see *Respiratory Depression*).

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

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of TEMGESIC but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease, asthma, sleep apnoea, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia), hepatic impairment (see *Use in hepatic impairment*) and severe renal impairment (see *Use in renal impairment*). Opioids should be used with caution and with close monitoring in these patients (see section *4.2 Dose and method of administration*). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section *4.3 Contraindications*).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variations in response.

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.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma, and death. Because of these risks, the concomitant prescribing of TEMGESIC with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally active antiemetics and other CNS depressants should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe TEMGESIC concomitantly with any of the medicines, the lowest effective dose should be used and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking TEMGESIC.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)

Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not

recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

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.

When discontinuing TEMGESIC in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids* and section *4.2 Dose and Method of Administration*).

Accidental ingestion/exposure

Accidental ingestion or exposure of TEMGESIC, especially by children, can result in a fatal overdose of buprenorphine. Patients and their caregivers should be given information on safe storage and disposal of unused TEMGESIC (see section *6.4 Special precautions for storage* and section *6.6 Special precautions for disposal*).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse

sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see *Tolerance, dependence and withdrawal*). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see section *4.2 Dose and Method of Administration*). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

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.

Use in hepatic Impairment

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

Use in renal impairment

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.

Paediatric Use

TEMGESIC is not recommended for use in children.

Effects on Laboratory Tests

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

4.5 Interaction with other medicines and other forms of interaction

Benzodiazepines and other CNS depressants

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 (see section *4.4 Special warnings and precautions for use – Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol*).

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see Section 4.4 Warnings and Precautions).
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

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 - Tolerance, Dependence and Withdrawal*).

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. It recommended that patients receiving TEMGESIC should be closely monitored if inducers are co-administered and the dose of buprenorphine or CYP3A4 inducer may need to be adjusted accordingly.

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.

Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue buprenorphine if serotonin syndrome is suspected. Examples of serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, serotonin precursors (e.g. tryptophan), drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol, lithium, St. John's wort), certain muscle relaxants (i.e. cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

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 1.6 mg/day. Evidence for teratology was not evident in animal studies.

Maternal oral administration at high doses (80 mg/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 8 mg/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 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 Nervousness Depression Psychotic disorder Hallucination Depersonalisation	Dysphoria Agitation
Nervous system disorders			
Sedation Dizziness Drowsiness Sleep	Headache	Dysarthria Paraesthesia Coma Tremor	Convulsion Coordination abnormal

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)**
Eye disorders			
	Miosis	Vision blurred Diplopia Visual impairment Conjunctivitis Amblyopia	
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 Flushing/warmth Chills/cold Dreaming	Injection site reaction

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	
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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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

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 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids, ATC code: N02AE01.

Mechanism 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 ƙ-opioid receptor.

Clinical Trials

No data available.

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 are essentially identical. The buprenorphine plasma level data achieved after these doses most closely fit a triexponential decay curve, with a very fast initial distribution phase (t½ 2 minutes) and a slow elimination phase (t½ approximately 5 hours).

At therapeutic doses the medicine 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 is recovered in the faeces and 27% in the urine. Metabolism of buprenorphine is predominantly in the liver, with the principal metabolites being the N-dealkylated product and its glucuronide, together with glucuronides of the parent medicine. Excretion is predominantly by the biliary route with some evidence for enterohepatic cycling following intestinal deconjugation.

5.3 Preclinical safety data

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 equianalgesic 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 0.01–30 mg/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 1.2 mg, 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 7 mg i.v. (equivalent to 200 mg 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 medicines likely to be used concurrently, such as halothane, fluothane and thiopentone sodium.

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

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

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C and out of reach of children. Protect from light

6.5 Nature and contents of container

Clear glass snap-1 mL ampoules in packs of 5.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Controlled Drug C4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

24 May 1979

10 DATE OF REVISION OF THE TEXT

9 August 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatting to new template
4.4 4.5	Information on opioids and benzodiazepines
4.3 5.3	Editorial change only from opiate to opioid
 4.1 4.3 4.4	Addition of Black Box Warning for Prescription Opioids Limitation of use to severe pain Addition of contraindications for respiratory conditions Rewording of sections Hazardous and Harmful Use - Respiratory Depression - Use of benzodiazepines. Addition of information under new headings: Use

	in Chronic Non Cancer Pain - Tolerance and Withdrawal - Accidental Ingestion/Expsoure- Hyperalgesia - Ceasing opioids.
4.5	Addition of information on Serotonergic drugs.
5.1	Inclusion of headings Mechanism of Action and Clinical Trials
5.3	Addition of genotoxicity and carcinogenicity.
6.2	Rewording of information on Incompatibilities