1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS **S6**

PROPRIETARY NAME AND DOSAGE FORM

TEMGESIC® Sublingual Tablets

TEMGESIC® 1 ml Injection

COMPOSITION

Each TEMGESIC Sublingual Tablet contains 0,2 mg buprenorphine (as hydrochloride).

Inactive ingredients include citric acid anhydrous, magnesium stearate, maize starch, mannitol, povidone and sodium citrate.

Contains lactose monohydrate.

Each 1 ml of TEMGESIC Injection contains 0,3 mg buprenorphine (as hydrochloride) in a 5 % dextrose solution.

PHARMACOLOGICAL CLASSIFICATION

A.2.9 Other Analgesics

PHARMACOLOGICAL ACTION

Buprenorphine hydrochloride is an opiate analgesic agent whose pharmacological effects in animals include narcotic agonist and antagonist activity.

INDICATIONS

For short term use in patients suffering from moderate to severe pain.

CONTRAINDICATIONS

TEMGESIC should not be used in patients with severe hepatic insufficiency, impaired respiratory function and should not be used in patients with acute asthma, or in patients who have shown

hypersensitivity to this medication or to other centrally-acting analgesics. The use of TEMGESIC is not recommended during pregnancy.

TEMGESIC should not be used during labour as it may cause irreversible respiratory depression in the newborn.

WARNINGS AND SPECIAL PRECAUTIONS

Special care must be exercised in the elderly where respiratory capacity may be reduced.

TEMGESIC may cause severe respiratory depression which may not be completely reversed by opiate antagonists.

Respiratory depression: Respiratory depression may occur within the recommended therapeutic dose range in patients receiving TEMGESIC. Therefore, TEMGESIC should be used with caution in patients with impaired respiratory function, those with acute asthmatic attack, chronic obstructive pulmonary disease cor pulmonale, decreased respiratory reserve or those with pre-existing respiratory depression, hypoxia or hypercapnia. Caution is also advised if TEMGESIC is administered to patients taking drugs with respiratory depressant effects. In patients with these physical and/or pharmacological risk factors, the dose should be reduced by approximately one half.

Dependence Liability: TEMGESIC is a partial agonist of the morphine type i.e. it has pharmacological effects, which in certain individuals, chronic administration may lead to dependence; but at a lower level than a full agonist (e.g. morphine), due to an opiate-like euphoric component of the drug.

Withdrawal symptoms take several days to appear when TEMGESIC is withdrawn, thus, following chronic use, abrupt discontinuation of treatment is not recommended.

TEMGESIC should be prescribed and administered with caution to patients with a history of drug abuse and to patients with emotional instability. In susceptible patients, dependence may lead to self-administration of the drug when pain no longer exists. Patients must not exceed the dosage TEMGESIC prescribed, and patients should be urged to consult their doctor if other prescription medications are currently being used or are prescribed for future use. Special care must be exercised in the elderly where respiratory capacity may be reduced.

Use in opioid-dependent patients: Because TEMGESIC has narcotic antagonist properties, initial administration may precipitate withdrawal symptoms (similar to that associated with naloxone) in patients presenting with marked drug dependence on full opioid agonists such as methadone or heroin.

For the same reason it should be given with caution to patients previously treated with other narcotic analgesics. TEMGESIC is not recommended for patients who have developed physical dependence to narcotics except when TEMGESIC is administered within a framework of medical, social and psychological treatment.

Hepatic impairment: TEMGESIC is extensively metabolized by the liver and its clearance is related to hepatic blood flow. Decreased metabolism of TEMGESIC in patients with moderate and severe hepatic impairment may predispose such patients to an accentuation of drug effects at recommended therapeutic dosage, due to elevated plasma levels. Therefore, TEMGESIC should be administered with caution to patients with moderate to severe hepatic impairment and to those receiving other agents (e.g. halothane) that decrease hepatic clearance. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of TEMGESIC.

TEMGESIC has been shown to increase intracholedochal pressure to a similar degree as other opioid analgesics and therefore, TEMGESIC should be administered with caution to patients with biliary tract dysfunction.

Use in ambulatory patients: Caution and close patient observation are recommended when TEMGESIC is used in ambulatory patients. Since TEMGESIC may cause drowsiness or dizziness, and these could be potentiated by other centrally-acting agents, including alcohol, ambulant patients should be cautioned against engaging in activities requiring mental alertness, such as driving a car or operating machinery/appliances.

Interaction with other central nervous system depressants: Patients receiving TEMGESIC in the presence of other opioid 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.

Cardiovascular effects: TEMGESIC may cause a slight reduction in pulse rate and blood pressure in some patients. Like other opioids, TEMGESIC may produce orthostatic hypotension in ambulatory patients.

Head injury and increased intracranial pressure: TEMGESIC has the potential for elevating cerebrospinal fluid pressure. This effect, coupled with a respiratory depressant effect, may be markedly exaggerated in the presence of head injury, other intracranial lesions or when there is a pre-existing increase in cerebrospinal pressure. TEMGESIC can produce miosis and changes in the level of consciousness which may obscure the clinical course of patients with head injuries. Therefore, in such patients TEMGESIC should be used with caution.

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.

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

Other opioid class warnings: TEMGESIC should be administered with caution to elderly or debilitated patients and to those with severe impairment of renal function, myxoedema, or hypothyroidism, adrenal insufficiency (e.g. Addison’s disease), central nervous system depression or coma, toxic psychoses, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium tremens or kyphoscoliosis.

Effects on ability to drive and use machines: Low dose TEMGESIC may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants. Caution is advised when driving and using machines (see INTERACTIONS).

TEMGESIC should be administered for the relief of pain and not in anticipation of pain.

INTERACTIONS

Alcohol: TEMGESIC should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of TEMGESIC, which can make driving vehicles and operating machinery hazardous. (see WARNINGS AND SPECIAL PRECAUTIONS)

TEMGESIC should be used cautiously together with:

Benzodiazepines: This combination may potentiate respiratory depression of central origin, with risk of death; therefore, dosages must be limited. The risk of drug abuse should also be considered as a number of deaths and cases of coma have occurred when addicts have intravenously misused TEMGESIC and benzodiazepines concomitantly.

Respiratory and cardiovascular collapse has been reported in patients receiving therapeutic doses of diazepam and analgesic doses of TEMGESIC concomitantly; therefore, dosages must be limited and this combination must especially be avoided in cases where there is a risk of misuse. Patients must use benzodiazepines concurrently with this product only as prescribed (see WARNINGS AND SPECIAL PRECAUTIONS).

Other central nervous system depressants: other opioid derivatives (analgesics and antitussives); certain antidepressants, sedative H_1-receptor antagonists, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. This combination increases central nervous system depression and can make driving vehicles and operating machinery hazardous.

Monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.

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

Other opioid analgesics: The analgesic effects of full agonist opioids may be competitively diminished by the partial agonist TEMGESIC. For patients who have developed a physiological dependence to full opioid agonists, administration of the partial agonist TEMGESIC may elicit withdrawal symptoms (see WARNINGS AND SPECIAL PRECAUTIONS).

CYP3A4 inhibitors: Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, co-administration of medicines that inhibit CYP3A4 activity may result in increases in buprenorphine and norbuprenorphine concentrations. Thus patients receiving TEMGESIC co-administered with inhibitors of CYP3A4 such as gestodene, macrolide antibiotics (e.g. erythromycin, troleandomycin), azole antifungal agents (e.g. ketoconazole), or HIV protease inhibitors (e.g. ritanovir, indinavir and saquinavir) should be carefully monitored. Caution is advised when administering TEMGESIC to patients receiving these medications, and if necessary, dose adjustments should be considered.

CYP3A4 inducers: CYP450 inducers, such as phenobarbital, rifampicin, carbamazepine, and phenytoin, induce metabolism and may cause increased clearance of TEMGESIC. Caution is advised when administering TEMGESIC to patients receiving these medications, and if necessary, dose adjustments should be considered.

Other: Halothane is known to decrease hepatic clearance. 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 when used with halothane.

To date, no notable interaction has been observed with cocaine.

A suspected interaction between TEMGESIC and phenprocoumon resulting in purpura has been reported.

PREGNANCY AND LACTATION

The use of TEMGESIC is not recommended during pregnancy. Data is insufficient to evaluate the effects of TEMGESIC on pregnant women. At the end of pregnancy, high doses, even for a short duration of time, may induce respiratory depression in neonates. During the last three months of pregnancy, chronic use of TEMGESIC may be responsible for a withdrawal syndrome of neonates. Consequently, the use of TEMGESIC is not recommended during pregnancy.
In addition, because TEMGESIC passes into the mother's milk, breastfeeding is contra-indicated.

DOSAGE AND DIRECTIONS FOR USE

TEMGESIC Sublingual Tablets

Adults:

1 to 2 TEMGESIC tablets (0,2 to 0,4 mg buprenorphine) to be dissolved under the tongue every 6 to 8 hours or as required. The tablet may require 5 to 10 minutes to dissolve and should not be chewed or swallowed. Where rapid pain relief is required this regimen should be preceded by an intramuscular or intravenous injection of TEMGESIC injection (0,3 mg/ml buprenorphine). The recommended starting dose for moderate to severe pain of the type typically presenting in general practice is one tablet 8 hourly.

TEMGESIC Injection

Adults:

The recommended dosage is 0,3 to 0,6 mg by intramuscular or slow intravenous injection, repeated every 6 to 8 hours or as required.

Elderly: Dosage adjustments of buprenorphine in patients over 65 years of age are generally unnecessary; however, with increasing age, increasing care should be taken when administering TEMGESIC.

Hepatic Impairment: As TEMGESIC pharmacokinetics may be altered in patients with hepatic impairment, lower initial doses and careful dose titration in patients with hepatic impairment may be required (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal Impairment: Modification of the TEMGESIC dose is not generally required for patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (CLcr < 30 ml/min), which may require dose adjustment (see WARNINGS AND SPECIAL PRECAUTIONS).

Paediatric population: TEMGESIC Sublingual Tablets and Injection are not recommended for use in children.

SIDE EFFECTS

Clinical Trial Data:

Table 1: Treatment – Related Side-Effects Reported by Body System 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)	
Psychiatric disorders Uncommon	 Euphoria, Psychosis, Confusional state, Nervousness, Depression, Hallucination, Depersonalisation
Nervous system disorders Very Common Common Uncommon Rare	 Sedation, Dizziness/vertigo Headache Weakness/fatigue, Slurred speech, Paraesthesis, Tinnitus, Coma, Tremor Dysphoria, Agitation, Convulsions, Lack of muscle coordination
Eye disorders Common Uncommon	 Miosis Diplopia, Visual abnormalities, Conjunctivitis

Vascular disorders	
Common	Hypotension
Uncommon	Hypertension, Pallor, Tachycardia, Bradycardia, Cyanosis, 2nd degree AV (atrioventricular) block
Respiratory, thoracic and mediastinal disorders	
Common	Hypoventilation
Uncommon	Dry mouth, Dyspnoea, Apnoea
Gastrointestinal disorders	
Very Common	Nausea
Common	Vomiting
Uncommon	Constipation, Dyspepsia, Flatulence
Rare	Loss of appetite, Diarrhoea
Skin and subcutaneous tissue disorders	
Common	Sweating
Uncommon	Pruritus, Rash
Rare	Urticaria
General disorders and administration site conditions	
Uncommon	Urinary retention, Malaise

Post-marketing Data:

Tabulated list of adverse reactions.

During use of TEMGESIC in treatment, the following adverse reactions have also been observed: Insomnia, drowsiness, fainting, orthostatic hypotension, respiratory depression, hepatic necrosis and hepatitis.

The following is a list of the most commonly reported adverse drug reactions reported during post-marketing surveillance. Events occurring in at least 1% of reports by healthcare professionals and considered expected, are included. Cases of bronchospasm, angioneurotic oedema and anaphylactic shock have also been reported and are included in Table 2.

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

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms:

The expected symptoms of overdosage are drowsiness, nausea, vomiting and respiratory depression; marked miosis may occur. Therapeutic doses may produce clinically significant respiratory depression in certain circumstances.

If tablets are swallowed, the absorbed active ingredient is metabolized by the liver more rapidly than if absorbed sublingually.

In the event of 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:

Symptomatic treatment of respiratory depression, following standard intensive care measures, should be performed. A patent airway and assisted or controlled ventilation must be assured.
The patient should be transferred to an environment within which full resuscitation facilities are available. 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. If an opioid antagonist (i.e. naloxone) is used, the long duration of action of TEMGESIC should be taken into consideration.

IDENTIFICATION

TEMGESIC Sublingual Tablets: A white bi-convex tablet engraved on one side with the letter “L”.

TEMGESIC 1 ml Injection: A colourless solution in clear glass ampoules of 1 ml.

PRESENTATION

TEMGESIC Sublingual Tablets:

Carton of 50 tablets, containing blister strips of 10 tablets each.

TEMGESIC 1 ml Injection:

A colourless solution in clear glass ampoules of 1 ml in packs of 5 ampoules.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from light and moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS

TEMGESIC Sublingual Tablets: S/2.7/327

TEMGESIC 1 ml Injection: L/2.9/157

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF REGISTRATION

TEMGESIC Sublingual Tablets: 11 December 1989

TEMGESIC 1 ml Injection: 18 April 1984

DATE OF PUBLICATION OF THIS PACKAGE INSERT

24 October 2014

COUNTRY REGISTRATION NUMBERS

TEMGESIC Sublingual Tablets; Botswana: BOT0400660 S2

TEMGESIC 1 ml Injection; Botswana: BOT0400659 S2