1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS S6

1. NAME OF THE MEDICINE

TEMGESIC Sublingual Tablets

TEMGESIC 1 ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Sugar content: Contains 29,842 mg lactose monohydrate

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

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with buprenorphine as in TEMGESIC in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology

TEMGESIC Sublingual Tablets

Adults:

1 to 2 TEMGESIC tablets (0,2 mg 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. Where rapid pain relief is required this regimen should be preceded by an intramuscular or intravenous injection of TEMGESIC 1 ml 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, repeated every 6 to 8 hours or as required.

Special populations

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 section 4.4).

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 section 4.4).

Paediatric population

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

Method of administration

TEMGESIC Sublingual Tablets

Administration is sublingual. The tablet should not be chewed or swallowed.

TEMGESIC Injection

Administration is by intramuscular or slow intravenous injection.

4.3 Contraindications

Hypersensitivity to buprenorphine or to any of the excipients listed in section 6.1.

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.

4.4 Special warnings and precautions for use

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicinal products:

Concomitant use of TEMGESIC and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe TEMGESIC concomitantly with sedative medicines, the lowest effective dose of the sedative medicines should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Serotonin syndrome:

Concomitant administration of TEMGESIC and other serotonergic medicines, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic medicines is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Seizures:

Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medicines, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic uses and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

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.

Drug withdrawal syndrome:

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with TEMGESIC.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this medicine during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction in opioid dose.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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.

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

Excipients:

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

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 section 4.4)

TEMGESIC should be used cautiously together with:

Serotonergic medicines: such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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 section 4.4).

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 section 4.4).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of TEMGESIC is not recommended during pregnancy.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding

Administration to nursing woman is not recommended as TEMGESIC may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

No data on male and female fertility is available.

4.7 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 section 4.5).

4.8 Undesirable 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)		
System organ class	***Frequency***	***Adverse Event***
Psychiatric disorders	Uncommon	Euphoria, Psychosis, Confusional state, Nervousness, Depression, Hallucination, Depersonalisation
	Frequency unknown	Drug dependence (see section 4.4)
Nervous system disorders	Very Common	Sedation, Dizziness/vertigo
	Common	Headache
	Uncommon	Weakness/fatigue, Slurred speech, Paraesthesis, Tinnitus, Coma, Tremor
	Rare	Dysphoria, Agitation, Convulsions, Lack of muscle coordination
	Frequency unknown	Seizures
Eye disorders	Common	Miosis
	Uncommon	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, drug withdrawal syndrome

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*

Table 2: Spontaneous Adverse Drug Reactions Reported by Body System	
MedDRA System Organ Class	**Preferred Term**
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.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous

Lactose monohydrate

Magnesium stearate

Maize starch

Mannitol

Povidone

Sodium citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

TEMGESIC Sublingual Tablets:

Nylon/aluminium/uPVC blister pack: 3 years

HDPE bottle: 3 years

TEMGESIC 1 ml Injection:

3 years packed in a 1 ml Type I neutral flint glass ampoule.

6.4 Special precautions for storage

TEMGESIC Sublingual Tablets:

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

TEMGESIC 1 ml Injection:

Store at or below 30 °C.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

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Johannesburg, 2013

Tel: +27 11 494 8000

8. REGISTRATION NUMBER(S)

TEMGESIC Sublingual Tablets: S/2.7/327

TEMGESIC 1 ml Injection: L/2.9/157

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

TEMGESIC Sublingual Tablets: 11 December 1989

TEMGESIC 1 ml Injection: 18 April 1984

10. DATE OF REVISION OF THE TEXT

08 February 2022

DETAILS OF REGISTRATION IN SSA COUNTRIES

TEMGESIC Sublingual Tablets; Botswana: BOT0400660 S2

TEMGESIC 1 ml Injection; Botswana: BOT0400659 S2