APPROVED PROPOSED PACKAGE INSERT:

TRAMADOL 50 mg AUSTELL CAPSULE

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

TRAMADOL 50 mg AUSTELL CAPSULES

COMPOSITION

Each capsule contains tramadol hydrochloride 50 mg.

Excipients:

Colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

Capsule Shell:

Ferric oxide yellow, gelatin, indigo carmine, methyl paraben, propyl paraben, sodium lauryl sulphate and titanium dioxide.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A.2.9 Other analgesics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Tramadol hydrochloride is a centrally-acting synthetic opioid analgesic binding to specific opioid receptors. It is a non-selective, pure agonist at mu (μ), delta (δ) and kappa (κ) opioid receptors with a higher affinity for the μ receptor. Other mechanisms which may contribute to its analgesic effect, are inhibition of neuronal re-uptake of noradrenaline and enhancement of serotonin release.

Tramadol hydrochloride does not promote histamine release.

Patients devoid of CYP2D6 may need higher doses of tramadol to achieve adequate analgesia.

Pharmacokinetic properties:

Tramadol hydrochloride is readily absorbed following oral administration. Oral bioavailability is approximately 68 % after a single dose and increases to 90 % at steady state. Onset of action is dose dependent but generally occurs within one hour of dosing, peaking within 2 to 3 hours. Duration of analgesia is about 6 hours. The rate or extent of absorption is not significantly affected by co-administration with food.

Tramadol hydrochloride is primarily metabolised in the liver (90 %) with one of its metabolites, mono-O-desmethyltramadol (M1), being 2 to 4 times as potent as the parent compound.

Tramadol hydrochloride has a linear pharmacokinetic profile within the therapeutic dosage range.

Tramadol hydrochloride and its metabolites are excreted mainly in the urine. The elimination half-life is 5 to 7 hours, but is prolonged in impaired hepatic and renal function.

Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

INDICATIONS

TRAMADOL AUSTELL is indicated for the management of moderate to moderately severe pain.

CONTRAINDICATIONS

Hypersensitivity to tramadol hydrochloride or opioids or any of the inactive ingredients.

Acute intoxication with alcohol, hypnotics, analgesic opioids or psychotropic medicines, due to the risk of respiratory depression.

Patients taking monoamine oxidase (MAO) inhibitors or within two weeks of their discontinuation (see INTERACTIONS).

Narcotic withdrawal treatment.

Respiratory depression especially in the presence of cyanosis and excessive bronchial secretions.

Increased intracranial pressure or central nervous depression due to head injury or cerebral disease.

TRAMADOL AUSTELL should not be used in pregnant and breastfeeding women (see PREGNANCY AND LACTATION).

TRAMADOL AUSTELL should not be given to patients with epilepsy who are not adequately controlled by treatment.

WARNINGS and SPECIAL PRECAUTIONS:

Avoid the use of **TRAMADOL AUSTELL** in patients with a history of addiction, as physical dependence of the morphine-type may develop. Reinstatement of physical dependence in patients that have previously been dependent, may occur with **TRAMADOL AUSTELL.**

TRAMADOL AUSTELL is not suitable for children under the age of 12 years.

Use with caution in patients with a history of epilepsy or those susceptible to seizures (e.g. patients taking neuroleptics and other medicines that reduce the seizure threshold).

Use with caution in patients with renal or hepatic impairment and avoid if severe.
The administration of **TRAMADOL AUSTELL** concurrently with other central nervous system medicines is likely to intensify and prolong CNS effects (see INTERACTIONS).

The possibility of respiratory depression cannot be excluded if the recommended dose is exceeded or other centrally depressant medicines are given concomitantly. **TRAMADOL AUSTELL** should not be used for the treatment of minor pain.

Effects on the ability to drive and use machines
Patients should be warned not to operate machinery or drive a car while using **TRAMADOL AUSTELL** as reaction time may be impaired. This applies particularly when **TRAMADOL AUSTELL** is used in conjunction with other psychotropic medicines, including alcohol.

INTERACTIONS

Monoamine oxidase inhibitors (MAOIs):

Because of its inhibitory effect on serotonin uptake, **TRAMADOL AUSTELL** should not be used concomitantly with MAOIs or within 14 days after discontinuing such treatment (see CONTRAINDICATIONS).

Central nervous system (CNS) depression-producing medicines, including alcohol and anaesthetics:

Caution is recommended when taking CNS depression-producing medicines including alcohol because concurrent use may potentiate the CNS depressant effects. The duration of anaesthesia may be prolonged when **TRAMADOL AUSTELL** is combined with barbiturates.

Carbamazepine:

Serum concentrations of **TRAMADOL AUSTELL** are reduced by carbamazepine, resulting in diminished analgesic activity of **TRAMADOL AUSTELL.**

CYP3A4 inhibitors:

Inhibitors of CYP3A4 such as ketoconazole and erythromycin may inhibit the metabolism of **TRAMADOL AUSTELL**

Ondansetron:

The antiemetic 5-HT3 antagonist ondansetron increases the requirement of **TRAMADOL AUSTELL** in patients with postoperative pain.

Coumarin derivatives:

Caution should be exercised during concomitant treatment with **TRAMADOL AUSTELL** and warfarin-like medicines due to reports of increased INR with major bleeding and ecchymoses in some patients.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established (see CONTRAINDICATIONS).

Pregnancy:

TRAMADOL AUSTELL crosses the placenta. The repeated administration of **TRAMADOL AUSTELL** during pregnancy may lead to withdrawal symptoms in the newborn.

Lactation:

TRAMADOL AUSTELL passes into breastmilk. Mothers on **TRAMADOL AUSTELL** should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE

The dosage should be adjusted to the intensity of pain and the individual's response to the analgesic action of **TRAMADOL AUSTELL**. **TRAMADOL AUSTELL** should not be used for the treatment of minor pain.

Adults and children over the age of 14 years:

Oral administration:

Moderate pain:

Initial dose of 50 mg, followed by 50 mg or 100 mg 4 – 6 hourly.

Severe pain:

Initial dose of 100 mg, followed by 50 mg or 100 mg 4 – 6 hourly.

A total oral daily dose of more than 400 mg per day must not be exceeded.

Elderly:

The usual doses may be used except in patients 75 years of age and over where a downward adjustment of the dose and/or prolongation of the interval between doses are recommended.

Renal impairment/ renal dialysis:

The elimination of tramadol may be prolonged. The usual initial dose should be used. For patients with creatinine clearance < 30 mℓ/min, the dosage interval should be increased to 12

hours. As tramadol is only removed very slowly by haemodialysis or haemofiltration, postdialysis administration to maintain analgesia is not usually necessary.

Hepatic impairment:

The elimination of **TRAMADOL AUSTELL** may be prolonged. The usual initial dose should be used but in severe hepatic impairment, the dosage interval should be increased to 12 hours.

SIDE EFFECTS

Immune system disorders

Less Frequent: Angioedema, bronchospasm, anaphylaxis and anaphylactoid reactions. These reactions may occur after the first dose.

Psychiatric disorders

Less Frequent: Confusion, hallucinations.

Nervous system disorders

Frequent: Dizziness, headache.

Less Frequent: Sedation, drowsiness, seizures (see WARNINGS AND SPECIAL PRECAUTIONS), amnesia, paraesthesia.

Eye Disorders

Less Frequent: Blurred vision, mydriasis.

Cardiac disorders

Less frequent: Bradycardia, tachycardia.

Vascular disorders

Less frequent: Flushing, syncope, postural hypotension, cardiovascular collapse.

Gastrointestinal disorders

Frequent: Nausea, vomiting, dry mouth, dyspepsia, constipation, diarrhoea, anorexia, abdominal pain.

Hepato-biliary disorders

Less frequent: Increase in liver enzymes.

Renal and urinary disorders

Less Frequent: Urinary retention, urinary frequency.

Skin and subcutaneous tissue disorders

Frequent: Sweating.

Less Frequent: Urticaria, vesicles, pruritus, skin rashes.

Toxic Epidermal Necrolysis and Steven-Johnsons Syndrome have been reported.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Muscular weakness.

General disorders and administrative site conditions

Less frequent: Fatigue.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdose:

(see SIDE EFFECTS)

Symptoms of overdosage are typical of opioids, and include pinpoint pupils, slow heartbeat, slow or troubled breathing, weakness, seizures, cold, clammy skin.

Treatment of overdose:

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted. Treatment of restlessness is symptomatic and supportive.

Naloxone should be used to reverse some, but not all, symptoms caused by overdosage with **TRAMADOL AUSTELL**. Administration of naloxone should be done with caution because it may precipitate seizures.

Diazepam has been found to be effective in treating convulsions caused by **TRAMADOL AUSTELL** toxicity.

Haemodialysis is not recommended in overdose, since it removes less than 7 % of the administered dose of **TRAMADOL AUSTELL** in a 4-hour dialysis period.

IDENTIFICATION

Green / Yellow coloured hard gelatin capsules, size '3' filled with a homogeneous white to off white powder.

PRESENTATION

Blister packs (White Opaque PVDC coated PVC film and Aluminium foil) of 1 x 10, 2 x 10 and 10 x 10 capsules.

STORAGE INSTRUCTIONS

Store in a cool dry place at or below 25 °C. Protect from light.

Keep the blister packs in carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

A40/2.9/0388

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd.

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