Approved Professional Information for Medicines for Human Use:

TRAMADOL SR 100 AUSTELL

TRAMADOL SR 200 AUSTELL

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TRAMADOL SR 100 AUSTELL 100 mg sustained release film-coated tablets

TRAMADOL SR 200 AUSTELL 200 mg sustained release film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRAMADOL SR 100 AUSTELL: Each sustained release film-coated tablet contains 100 mg tramadol hydrochloride.

TRAMADOL SR 200 AUSTELL: Each sustained release film-coated tablet contains 200 mg tramadol hydrochloride.

Contains sugar (lactose monohydrate).

TRAMADOL SR 100 AUSTELL (100 mg): 36 mg lactose monohydrate per tablet.

TRAMADOL SR 200 AUSTELL (200 mg): 20 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TRAMADOL SR 100 AUSTELL sustained release film-coated tablets. White to off white round, biconvex film-coated tablets with “100” embossed on one side and plain on other side.

TRAMADOL SR 200 AUSTELL sustained release film-coated tablets. Light orange to light pink, round, biconvex film-coated tablets with “200” embossed on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to severe pain.

4.2 Posology and method of administration

Posology

The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Adults and children over 12 years

The usual initial dose is 100 mg twice daily, to be taken whole, not divided or chewed, with sufficient liquid, with or without meals, preferably mornings and evenings. If pain relief is not adequate, the dose may be increased to 200 mg twice daily.

A total daily dose of 400 mg TRAMADOL SR AUSTELL should not be exceeded.

Dosage intervals can be adjusted to individual requirements but should be at least 8 hours.

The lowest effective analgesic dose should generally be selected.

Special populations

Elderly

A downward adjustment of the dose and/or prolongation of the interval between doses are recommended in the elderly (over 75 years).

Renal insufficiency/dialysis

In patients with renal insufficiency the elimination of tramadol hydrochloride is delayed. In these patient's prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal insufficiency TRAMADOL SR AUSTELL tablets are not recommended.

Patients with hepatic impairment

In patients with hepatic insufficiency the elimination of tramadol hydrochloride is delayed. In these patient's prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe hepatic insufficiency TRAMADOL SR AUSTELL tablets are not recommended.

Duration of treatment

Under no circumstances should TRAMADOL SR AUSTELL be given for longer than absolutely necessary. If the nature and severity of the disease requires long-term pain treatment, careful checks should be carried out initially and at regular intervals to assess efficacy and adverse events, and to what extent further treatment with TRAMADOL SR AUSTELL is necessary.

Paediatric population

On account of the dosage strength, TRAMADOL SR AUSTELL is not recommended for children below the age of 12 years.

Method of administration

TRAMADOL SR AUSTELL is indicated for oral administration.

The tablets are to be taken whole, not divided or chewed, with sufficient liquid, independent of meals, preferably mornings and evenings.

4.3 Contraindications

- Known hypersensitivity to tramadol hydrochloride or opioids or any of the ingredients of TRAMADOL SR AUSTELL (see section 4.4 and 4.5).
- In acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines (see section 4.4 and 4.5).
- It should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal (see section 4.5).
- TRAMADOL SR AUSTELL should not be given to patients with epilepsy.
- TRAMADOL SR AUSTELL must not be used for narcotic withdrawal treatment (see section 4.4 and 4.5).
- TRAMADOL SR AUSTELL should not be given to patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions (see section 4.4 and 4.5).
- TRAMADOL SR AUSTELL should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease (see section 4.4 and 4.5).
- TRAMADOL SR AUSTELL should not be used in pregnant and breastfeeding women (see section 4.6).

4.4 Special warnings and precautions for use

Tramadol may only be used with particular caution in opioid-dependent patients, patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure.

In patients sensitive to opiates tramadol should only be used with caution.

TRAMADOL SR AUSTELL should not be used in the treatment of minor pain.

CNS depressant medicine concomitant use

Respiratory depression may develop if the recommended dosages are exceeded or other centrally depressant medicines are given concomitantly. E.g., concomitant use of tramadol and sedating medicine such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with this sedating medicine should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe tramadol concomitantly with sedating medicine, the lowest effective dose of tramadol should be used, and the duration of the concomitant 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).

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant medicine are being administered (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the possibility of respiratory depression cannot be excluded in these situations.

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.

Seizures

Seizures have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicine that lowers the seizure threshold, e.g., in patients taking tricyclic anti-depressants or other tricyclic compounds such as promethazine, selective serotonin re-uptake inhibitors, MAO-inhibitors and neuroleptics (see section 4.5). The risk of seizures may also be increased in patients with epilepsy; with a history of seizures or in patients with a recognised risk for seizures e.g., drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramadol overdose.

Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Opioid dependence

Tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop, especially after long-term use.

Tramadol containing medicines such as TRAMADOL SR AUSTELL has been associated with craving drug-seeking behaviour and tolerance development. After discontinuation of TRAMADOL SR AUSTELL signs of withdrawal may appear. Symptoms of withdrawal syndrome similar to those occurring during opiate withdrawal, may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal symptoms.

Other symptoms that have been seen with tramadol discontinuation include panic attacks; severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

TRAMADOL SR AUSTELL should not be used in opioid-dependent patients. TRAMADOL SR AUSTELL can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence or who are chronically using opioids, treatment with TRAMADOL SR AUSTELL is not recommended (see section 4.5).

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalized pain (i.e., less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible.

Renal and hepatic impairment

TRAMADOL SR AUSTELL should be used with caution in patients with impairment of hepatic and renal function or in shock (see section 4.2)

CYP2D6 metabolism

Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme, an adequate analgesic effect may not be obtained. However, if the patient is an ultra-rapid metaboliser may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may lead to higher than expected serum M1 levels and there is a risk of developing side effects of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and even fatal (see section 4.8).

Children with compromised respiratory function

Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity (see section 4.3).

Hyponatraemia

Hyponatraemia has been reported with the use of tramadol, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatraemia. The hyponatraemia may be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and should resolve with discontinuation of tramadol and appropriate treatment (e.g. fluid restriction). During tramadol treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Excipients: lactose intolerance

This medicine contains lactose.

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

4.5 Interaction with other medicines and other forms of interaction

MAO inhibitors

Tramadol should not be combined with MAO inhibitors (see section 4.3).

It is reported that patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. Similar interactions with MAO inhibitors cannot be ruled out during treatment with TRAMADOL SR AUSTELL.

CNS depressants

Concomitant administration of tramadol with other centrally depressant medicine including alcohol may potentiate the CNS effects (see section 4.8 and 4.4).

The concomitant use of opioids with sedating medicine such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect.

The dose of tramadol and the duration of the concomitant use should be limited (see section 4.4).

Hepatic enzyme inhibitor/inducer

Reported pharmacokinetic study results have indicated that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.

Simultaneous or previous administration of carbamazepine (enzyme inducer) may reduce the analgesic effect and shorten the duration of action.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied (see section 4.8).

Seizures

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicine (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions (see section 4.4).

Serotonin toxicity

Concomitant therapeutic use of tramadol and serotonergic medicine, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity.

Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38˚C and inducible ocular clonus.

It is reported that withdrawal of the serotonergic medicine usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

The antiemetic 5-HT3 antagonist ondansetron increased the requirement of TRAMADOL SR AUSTELL in patients with postoperative pain. TRAMADOL SR AUSTELL may decrease the antiemetic efficacy of ondansetron.

Bleeding disorders

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy and lactation has not been established.

There is inadequate evidence available on the safety of tramadol in human pregnancy, Therefore, tramadol should not be used in pregnant

women. Animal studies with tramadol revealed at very high doses effects on organ development, ossification, and neonatal mortality. Tramadol crosses the placenta.

The repeated administration of TRAMADOL SR AUSTELL tablets during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see section 4.3)

Breastfeeding

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

Discontinuation of breastfeeding is generally not necessary following a single dose of tramadol.

Fertility

Animal studies did not show an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions, tramadol may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction with other psychotropic substances, particularly alcohol.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. Do not drive or use heavy machinery until you know how the medicine affects you.

4.8 Undesirable effects

The most frequently reported adverse reactions are nausea and dizziness.

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with tramadol hydrochloride.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Immune system disorders		Allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis	
Metabolism and nutrition disorders		Changes in appetite	Hypoglycaemia
Psychiatric disorders		Hallucinations, confusion, sleep disturbance, delirium,	

		anxiety and nightmares. Mood changes (usually elation, occasionally dysphoria), changes in activity (usually suppression, occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour, perception disorders). Medicine dependence may occur. Symptoms of withdrawal syndrome, similar to symptoms occurring during opiate withdrawal, including agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other	

		symptoms that have very rarely been seen with tramadol discontinuation include panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus, and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia)	
Nervous system disorders	Dizziness, headache, somnolence.	Speech disorders, paraesthesia, tremor, epileptiform convulsions, involuntary muscle contractions, abnormal coordination, syncope, convulsions/seizures (see sections 4.4 and 4.5)	
Eye disorders		Miosis, mydriasis, blurred vision	

Cardiac disorders		Cardiovascular regulation (palpitation, tachycardia), bradycardia	
Vascular disorders		Cardiovascular regulation (postural hypotension or cardiovascular collapse)	
Respiratory, thoracic and mediastinal disorders		Respiratory depression, dyspnoea (see section 4.5.) Worsening of asthma	
Gastrointestinal disorders	Nausea, constipation, dry mouth, vomiting	Retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea	
Hepatobiliary disorders		Increased liver enzyme values.	
Skin and subcutaneous tissue disorders	Hyperhidrosis	Dermal reactions (e.g. pruritus, rash, urticaria)	

Musculoskeletal and connective tissue disorders		Motorial weakness	
Renal and urinary disorders		Micturition disorders (dysuria and urinary retention)	
General disorders and administration site conditions	Fatigue		
Investigations		Increased blood pressure	

Description of selected adverse reactions

Cases of hypernatremia and/or SIADH have been reported in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medications that may cause hyponatremia.

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 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

4.9 Overdose

Symptoms

In principle, on intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions, and respiratory depression up to respiratory arrest.

Treatment

The general emergency measures apply. Keep open the respiratory tract (prevent aspiration), maintain respiration and circulation depending on the symptoms. The antidote for respiratory depression is naloxone. In animal experiments naloxone had no effect on convulsions. In such cases diazepam should be given intravenously.

In case of intoxication orally, gastrointestinal decontamination with activated charcoal is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolonged-release formulations.

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore, treatment of acute intoxication with TRAMADOL SR AUSTELL with haemodialysis or haemofiltration alone is not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.2.9. Other analgesics

Pharmacotherapeutic group: other opioids

ATC Code: N02 AX02

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

The relationship between serum concentrations and the analgesic effect is dose-dependent but varies considerably.
Patients devoid of CYP2D6 may need higher doses of tramadol, to achieve adequate analgesia.

5.2 Pharmacokinetic properties

Under steady state conditions the following was observed for tramadol in a sustained release preparation:

After oral administration of TRAMADOL SR AUSTELL, tramadol is absorbed.

The absolute bioavailability is approximately 70 % following a single dose and increases to approximately 90 % at steady state. C_{max} (141 ± 40 ng/mL) is reached 4.9 hours after oral administration of TRAMADOL SR AUSTELL (100 mg) and 4.8 hours (C_{max} 260 ± 62 ng/mL) after oral administration of TRAMADOL SR AUSTELL (200 mg).

Tramadol has a linear pharmacokinetic profile within the therapeutic dosage range. The elimination half-life is 5 to 7 hours. Tramadol is mainly metabolised in the liver (90 %).

Tramadol hydrochloride and its metabolites are almost completely excreted by the renal route (95 %). Biliary excretion of these components is quantitatively insignificant and is therefore subject to hepatic metabolism and renal elimination. The terminal half-life ($t_{½,\beta}$) is prolonged in impaired hepatic or renal function. In patients with liver cirrhosis, the mean $t_{½,\beta}$ of tramadol was 13,3 ± 4,9 h, $t_{½,\beta}$ / M1 18,5 ± 9,4 h, in patients with renal insufficiency (creatinine clearance ≤ 5 mL/min) the values were 11,0 ± 3,2 h (tramadol) and 16,9 ± 3,0 h (M1) respectively.

The inhibition of one or both types of isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal anhydrous silica (Aerosil 200)

Hypromellose (Methocel K15 Premium)

Isopropyl alcohol

Lactose monohydrate

Magnesium stearate (Veg. grade)

Microcrystalline cellulose (Avicel PH 101)

Film coating

Colour quinoline yellow E104

Ferric oxide red E172

Hypromellose (15 cps)

Macrogol 6000

Purified talc

Titanium dioxide E171

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

TRAMADOL SR AUSTELL slow sustained release film-coated tablets are packed in white opaque PVC (250 µ) / aluminium (0.025 mm) blisters of 10 tablets. The blisters are then packaged in an outer carton containing 30 or 60 tablets.

The outer carton is a folding board both side open box with aqueous varnish.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

TRAMADOL SR 100 AUSTELL: 50/2.9/0163

TRAMADOL SR 200 AUSTELL: 50/2.9/0164

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2022.05.18

10. DATE OF REVISION OF THE TEXT

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