Approved Professional Information for Medicines for Human Use:

EPSTELL

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

EPSTELL 50 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EPSTELL 50 mg Capsules

Each capsule contains 50 mg tramadol hydrochloride.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

EPSTELL 50 mg Capsules

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

In principle, the lowest pain-relieving dose should be selected. In general, a total oral daily dose of 400 mg of Tramadol (equivalent to 8 EPSTELL capsules) should not be exceeded.

The recommended dosages are guidelines.

EPSTELL capsules should be taken as follows:

Adults and children over 12 years

Moderate pain: Initial dose of 50 mg of Tramadol (1 EPSTELL capsule), 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.

Special populations

Elderly population

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

Renal impairment

In patients with renal insufficiency, the elimination of tramadol hydrochloride, as in EPSTELL is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal insufficiency EPSTELL capsules are not recommended.

Hepatic impairment

In patients with hepatic insufficiency the elimination of tramadol hydrochloride, as in EPSTELL is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe hepatic insufficiency EPSTELL capsules are not recommended.

Paediatric population

On account of the high dosage strength, EPSTELL capsules are not intended for children below the age of 12 years.

Duration of treatment

Under no circumstances should EPSTELL capsules be given for longer than absolutely necessary. If the nature and severity of the disease require 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 EPSTELL capsules is necessary.

Method of administration

Capsules are to be taken whole, not divided or chewed, with sufficient liquid, with or without food.

4.3 Contraindications

- Hypersensitivity to the tramadol hydrochloride or opioids or any of the excipients listed in section 6.1.
- All children younger than 12 years of age (See section 4.4)
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.
- In acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines.
- It should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.
- EPSTELL capsules should not be given to patients with epilepsy.
- EPSTELL capsules must not be used for narcotic withdrawal treatment.
- EPSTELL capsules should not be given to patients with respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.
- EPSTELL capsules should not be given to patients with increased intracranial pressure or central nervous depression due to head injury or cerebral disease.

- EPSTELL capsules 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 the product should only be used with caution.

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

Convulsions 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 medicines that lowers the seizure threshold (see section 4.5). Patients with epilepsy or those susceptible to seizures should be only treated with tramadol if there are compelling circumstances.

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant medicines 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 apnea (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.

Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic medicines or tramadol alone (see sections 4.5, 4.8 and 4.9).

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

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

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 or ocular clonus

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic medicines usually brings about a rapid improvement.

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 past 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 medications, 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 use 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 EPSTELL 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.

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 EPSTELL.

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 medicine 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 EPSTELL during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

EPSTELL is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

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 of opioid as in EPSTELL dose.

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 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 very rarely fatal.

Hyponatraemia

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

Adrenal insufficiency

Opioid analgesics as in EPSTELL may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Paediatric population

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

Post-operative use in children

There have been reports in the published literature that tramadol as in EPSTELL given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events. Extreme caution should be exercised when EPSTELL is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function

EPSTELL 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.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs):

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

In 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. The same interactions with MAO inhibitors cannot be ruled out during treatment with EPSTELL.

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

Concomitant administration of EPSTELL with other centrally depressant medicines including alcohol may potentiate the CNS effects (see section 4.8).

Sedating medicines

The concomitant use of opioids with sedating medicines 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 EPSTELL and the duration of the concomitant use should be limited (see section 4.4).

Cimetidine

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.

Carbamazepine

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

Serotonergic medicines

Tramadol as in EPSTELL 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 medicines (such as bupropion, mirtazapine, tehrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol as in EPSTELL and serotonergic medicines, 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 syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

Coumarin derivatives

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

CYP3A4 inhibitors

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol as in EPSTELL (N-demethylation) probably also the metabolism of the active 0-demethylated metabolite. The clinical importance of such an interaction has not been studied (see section 4.8).

Ondansetron

In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy and lactation has not been established. Therefore, EPSTELL capsules should not be used in pregnant women. EPSTELL crosses the placenta. Animal studies with EPSTELL revealed effects on organ development, ossification and neonatal mortality.
The administration of EPSTELL capsules during pregnancy may lead to habituation in the unborn child. The child may experience withdrawal symptoms after birth (see section 4.3).

Breastfeeding

EPSTELL passes into breastmilk. Mothers on EPSTELL should not breastfeed their infants.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

EPSTELL may cause effects such as somnolence and dizziness and therefore may impair the reactions of drivers and machine operators. This applies particularly in conjunction and other psychotropic substances, particularly alcohol.

4.8 Undesirable effects

Summary of the safety profile

The frequent side effects during treatment with Tramadol as in EPSTELL are nausea and dizziness.

a) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket 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		confusion, hallucinations sleep disturbance, delirium, anxiety and	drug dependence

		nightmares. Changes in mood (euphoria, dysphoria), decreased activity, restlessness and changes in cognitive and sensorial capacity (such as decision behaviour, perception disorders).	
Nervous system disorders	Dizziness, headache, somnolence	Sedation, drowsiness, seizures (see section 4.4), amnesia, paraesthesia. speech disorders, tremor, involuntary muscle contraction, abnormal coordination, syncope.	Serotonin syndrome
Eye disorders		Blurred vision, mydriasis, miosis	
Cardiac disorders		Bradycardia, tachycardia, dysrhythmias, palpitation	

Vascular disorders		Flushing, syncope, postural hypotension, cardiovascular collapse, increase in blood pressure.	
Respiratory, thoracic and mediastinal disorders		respiratory depression, dyspnoea, bronchospasm	Hiccups
Gastrointestinal disorders	Nausea, vomiting, dry mouth, dyspepsia, constipation	retching, gastrointestinal discomfort (a feeling of pressure in the stomach, bloating), diarrhoea.	
Hepatobiliary disorders		Increase in liver enzymes (Alanine transaminase-ALT; Aspartate transaminase-AST)	
Skin and subcutaneous tissue disorders	hyperhidrosis	dermal reactions (e.g. pruritus, rash, urticaria) Stevens Johnson Syndrome, Toxic Epidermal Necrolysis.	

Musculoskeletal and connective tissue disorders		Muscular weakness	
Renal and urinary disorders		micturition disorders (dysuria and urinary retention)	
General disorders and administration site conditions	Fatigue	drug withdrawal syndrome #	

Cases of hyponatraemia 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 hyponatraemia.

Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal, may occur as follows:
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, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

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

Signs and symptoms

On intoxication with tramadol symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.
Serotonin syndrome has also been reported.

Treatment of overdose

The general emergency measures apply. Keep open the respiratory tract (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 formulation.

Tramadol is minimally eliminated from the serum by haemodialysis or haemo-filtration. Therefore, treatment of acute intoxication with EPSTELL this medic 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 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.

5.2 Pharmacokinetic properties

Absorption

After oral administration of EPSTELL capsules, tramadol hydrochloride is absorbed with an absorption half-life ($t_{½\ ka}$) of 0,38 ± 0,18 hours. The mean systemic bioavailability is 68 %, independent of food intake.

Distribution

The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably. Patients devoid of CYP206 may need higher doses of tramadol, to achieve adequate analgesia.

Biotransformation

The inhibition of one or both types of isoenzymes CYP3A4 and CYP206 involved in the biotransformation of tramadol may affect the plasma concentration of tramadol or its active metabolite. Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

Elimination

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule powder

Colloidal silicon dioxide

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

Capsule shell

Ferric oxide yellow

Gelatin

Indigo carmine

Methyl paraben

Propyl paraben

Sodium lauryl sulphate

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dezzo Trading 392 (Pty) Ltd

Jespan Centre, Corner Garrick & Flagtail Street

Extension 8

Lenasia, 1821

Tel: +27 87 405 9660

8. REGISTRATION NUMBER

EPSTELL 50 mg capsules: 56/2.9/1059

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 October 2022

10. DATE OF REVISION OF THE TEXT