Professional information for TRAMAZAC 50

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TRAMAZAC 50, capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg tramadol (as tramadol hydrochloride).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

Size 2 locked hard gelatine capsule with a green cap and green body, containing white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of moderate to moderately severe pain.

4.2 Posology and method of administration

Posology

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 TRAMAZAC 50 capsules) should not be exceeded. The recommended dosages are guidelines.

TRAMAZAC 50 should be taken as follows:

Adults and children over 12 years

Moderate pain:

Initial dose of 50 mg of tramadol (one TRAMAZAC 50 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 patients

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

Patients with renal insufficiency/dialysis

In patients with renal insufficiency, the elimination of tramadol hydrochloride 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 TRAMAZAC 50 is not recommended.

Patients with hepatic impairment

In patients with hepatic insufficiency the elimination of tramadol hydrochloride 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 TRAMAZAC 50 is not recommended.

Duration of treatment

Under no circumstances should TRAMAZAC 50 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 TRAMAZAC 50 is necessary.

Paediatric population

On account of the high dosage strength, TRAMAZAC 50 is not intended for children below the age of 12 years.

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 tramadol hydrochloride, opioids or to any of the excipients of TRAMAZAC 50 listed in section 6.1.
- Acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicines (due to the risk of respiratory depression).
- Patients taking monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal (see section 4.5).
- For use in narcotic withdrawal treatment.
- Respiratory depression, or in the presence of cyanosis and excessive bronchial secretions.
- Increased intracranial pressure or central nervous depression due to head injury or cerebral disease.
- Children younger than 12 years of age (see sections 4.2 and 4.4).
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

- Epilepsy.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Seizures

Seizures/convulsions have been reported at therapeutic doses and the risk of seizures may be increased in patients exceeding the usual upper daily dose limit. TRAMAZAC 50 may increase the seizure risk in patients taking neuroleptics and other medicines that lowers the seizure threshold (see section 4.5). Patients with epilepsy should not take TRAMAZAC 50 (see section 4.3).

Shock

TRAMAZAC 50 should be used with caution in patients in shock.

Central nervous system (CNS) depressants

Concomitant use of TRAMAZAC 50 and sedating medicines such as benzodiazepines or related substances, may result in sedation, respiratory depression, coma and death. The administration of TRAMAZAC 50 concurrently with other central nervous system medicines is likely to intensify and prolong CNS effects (see section 4.5). 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 TRAMAZAC 50 concomitantly with sedating medicines, the lowest effective dose of TRAMAZAC 50 should be used, and the duration of the concomitant treatment should be as short as possible. The patients should be monitored 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).

Sleep-related breathing disorders

Opioids, such as TRAMAZAC 50, may 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.

Serotonin syndrome

TRAMAZAC 50 alone or in combination with other serotonergic medicines may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.5, 4.8 and 4.9).

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

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. Withdrawal of the serotonergic medicines usually brings about a rapid improvement.

Risk of tolerance, dependence and withdrawal symptoms

Tolerance, psychic and physical dependence may develop, especially after long-term use. At therapeutic doses, TRAMAZAC 50 has the potential to cause withdrawal symptoms. Symptoms of medicine 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 been seen with TRAMAZAC 50 discontinuation include: panic attacks; severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation and paranoia). Rarely cases of dependence and abuse have been reported. Because of this potential, the clinical need for continued analgesic treatment should be reviewed regularly. When a patient no longer requires therapy with TRAMAZAC 50, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

In patients with a tendency to medicine abuse or dependence, treatment should be for short periods and under strict medical supervision.

TRAMAZAC 50 is not a suitable substitute in opioid-dependent patients. TRAMAZAC 50 does not suppress morphine withdrawal symptoms although it is an opioid agonist.

Opioid-sensitive patients

TRAMAZAC 50 should be used with care in patients with increased reactivity to opioids.

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid, such as TRAMAZAC 50, 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 generalised 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 TRAMAZAC 50 should be reduced or tapered off, if possible.

CYP2D6 metabolism

Tramadol, as in TRAMAZAC 50, 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 of the CYP2D6 enzyme, there is a risk of developing side effects of opioid toxicity even within the recommended dosage range.

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.

Renal or hepatic impairment

TRAMAZAC 50 should be used with caution in patients with renal or hepatic impairment and avoided if severe (see section 4.2).

Adrenal insufficiency

Opioid analgesics, such as TRAMAZAC 50, may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite and weight loss.

Hyponatraemia

Hyponatraemia may occur with the use of TRAMAZAC 50, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medicines that may cause hyponatraemia. This hyponatraemia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolves with discontinuation of TRAMAZAC 50 and appropriate treatment (e.g. fluid restriction). During TRAMAZAC 50 treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Minor pain

TRAMAZAC 50 should not be used for the treatment of minor pain.

Paediatric population

Children under 12 years

TRAMAZAC 50 is not suitable for children under the age of 12 years (see sections 4.2 and 4.3).

Post-operative use in children

TRAMAZAC 50 should not be given post-operatively to children (under 18 years of age) after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea or for post-operative pain relief as it may lead to rare, but life-threatening adverse events (see section 4.3).

Children with compromised respiratory function

TRAMAZAC 50 is not recommended for use in children in whom respiratory function may be compromised, including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)

Because of its inhibitory effect on serotonin uptake, TRAMAZAC 50 should not be used concomitantly with MAOIs or within 14 days after discontinuing such treatment (see section 4.3), as life-threatening interactions on the central nervous system, respiratory and circulatory function may occur.

Central nervous system (CNS) depressants

Concomitant administration of TRAMAZAC 50 with other CNS depressants, including alcohol and anaesthetics, may potentiate the CNS depressant effects (see section 4.4). The duration of anaesthesia may be prolonged when TRAMAZAC 50 is combined with barbiturates.

The concomitant use of opioids, such as TRAMAZAC 50, with sedating medicines (e.g. benzodiazepines or related substances) increases the risk of sedation, respiratory depression, coma and death because of the additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Serotonergic medicines

Concomitant therapeutic use of TRAMAZAC 50 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, 4.8 and 4.9).

Seizure threshold-lowering medicines

TRAMAZAC 50 can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicines (such as neuroleptics, bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions (see section 4.4).

Anticoagulants

Caution should be exercised during concomitant treatment with TRAMAZAC 50 and anticoagulants (e.g. warfarin) as it may cause increased International Normalised Ratio (INR) with major bleeding and ecchymoses.

CYP3A4 inhibitors

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, may inhibit the metabolism of tramadol, as in TRAMAZAC 50, probably also the metabolism of the active *O*-demethylated metabolite.

Carbamazepine

Administration of TRAMAZAC 50 with carbamazepine (enzyme inducer) may reduce the serum concentrations, lower the analgesic effect and shorten the duration of action of TRAMAZAC 50.

Ondansetron

The antiemetic 5-HT3 antagonist ondansetron may increase the requirement of TRAMAZAC 50 in

patients with postoperative pain. TRAMAZAC 50 may decrease the antiemetic efficacy of ondansetron.

4.6 Fertility, pregnancy and lactation

TRAMAZAC 50 is contraindicated during pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

TRAMAZAC 50 may cause side effects, such as somnolence and dizziness (see section 4.8) and therefore affect the ability to drive a vehicle or use machinery. This applies particularly in conjunction with other psychotropic medicines, including alcohol. Caution is advised before driving a vehicle or operating machinery until the effects of TRAMAZAC 50 are known.

4.8 Undesirable effects

Summary of the safety profile

The most frequent side effects during treatment with TRAMAZAC 50 are nausea and dizziness, both occurring in more than 10 % of patients.

List of adverse reactions

Immune system disorders

Less frequent: allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioedema, worsening of asthma) and anaphylaxis. These reactions may occur after the first dose.

Metabolism and nutrition disorders

Frequent: anorexia.

Less frequent: changes in appetite.

Frequency unknown: hypoglycaemia, hyponatraemia.

Psychiatric disorders

Less frequent: hallucinations, confusion, sleep disturbances, delirium, anxiety and nightmares. Changes in mood (euphoria, dysphoria), decreased activity, restlessness and changes in cognitive and sensorial capacity (such as decision behaviour, perception disorders), medicine dependence, withdrawal reactions (see section 4.4).

Nervous system disorders

Frequent: sedation, somnolence, dizziness, headache.

Less frequent: speech disorders, paraesthesia, amnesia, tremor, convulsions, involuntary muscle contractions, abnormal coordination, syncope. Convulsions occur mainly after administration of high doses or after concomitant treatment with medicines which can lower the seizure threshold (see sections 4.4 and 4.5).

Frequency unknown: serotonin syndrome.

Eye disorders

Less frequent: miosis, mydriasis, blurred vision.

Cardiac disorders

Less frequent: bradycardia, tachycardia, palpitations, dysrhythmias.

Vascular disorders

Less frequent: flushing, postural hypotension, cardiovascular collapse, increase in blood pressure.

Respiratory, thoracic and mediastinal disorders

Less frequent: respiratory depression, dyspnoea, bronchospasm.

Frequency unknown: hiccups.

Gastrointestinal disorders

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

Less frequent: retching, gastrointestinal discomfort.

Hepatobiliary disorders

Less frequent: increase in liver enzymes (ALT and AST).

Skin and subcutaneous tissue disorders

Frequent: hyperhidrosis, dermal reactions (e.g. pruritis, rash).

Less frequent: vesicles, urticaria, toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported.

Musculoskeletal and connective tissue disorders

Less frequent: muscular weakness.

Renal and urinary disorders

Less frequent: micturition disorders (dysuria, urinary retention and urinary frequency).

General disorders and administration site conditions

Frequent: fatigue.

Description of selected adverse reactions

Hyponatraemia:

Hyponatraemia and/or SIADH may occur with TRAMAZAC 50, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medicines that may cause

hyponatraemia (see section 4.4).

Post-marketing experience

The following side effects have been reported for opioid containing medicines such as contained in TRAMAZAC 50:

Gastrointestinal disorders: Increased risk of abdominal pain, including pancreatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TRAMAZAC 50 is important. It allows continued monitoring of the benefit/risk balance of TRAMAZAC 50. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (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

Following an overdose with TRAMAZAC 50, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular constriction of the pupil of the eye, vomiting, cardiovascular collapse, consciousness disorders, coma, convulsions, respiratory depression and respiratory arrest.

Serotonin syndrome has also been reported (see section 4.4).

Treatment

The general emergency measures apply. Keep open the respiratory tract, maintain respiration and circulation depending on the symptoms. Suitable measures should be taken to avoid aspiration dangers.

Treatment of restlessness is symptomatic and supportive.

Respiratory depression can be antagonised with a pure opiate antagonist (naloxone). Administration of naloxone should be done with caution because it may precipitate seizures.

Convulsions should be treated with intravenous diazepam.

Gastrointestinal decontamination with activated charcoal is only recommended within 2 hours after TRAMAZAC 50 intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities.

Tramadol, as in TRAMAZAC 50, is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with TRAMAZAC 50 with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other analgesics.

Pharmacotherapeutic group: Analgesic.

ATC code: N02AX02.

Mechanism of action

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 norepinephrine (noradrenaline) and enhancement of serotonin release.

Tramadol hydrochloride does not promote histamine release.

5.2 Pharmacokinetic properties

Absorption

Tramadol hydrochloride is readily absorbed following oral administration with an absorption half-life ($t_{½\,ka}$) of 0,38 ± 0,18 hours. 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.

Distribution

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.

Biotransformation

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. Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite mono-*O*-desmethyltramadol (M1).

Elimination

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.

Biliary excretion of these components is quantitatively insignificant and is therefore subject to

hepatic metabolism and renal elimination. In patients with liver cirrhosis, elimination half-lives of 13,3 ± 4,9 h (tramadol) and 18,5 ± 9,4 h (*O*-desmethyltramadol), have been determined. 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 contents

Dibasic calcium phosphate

Magnesium stearate

Microcrystalline cellulose.

Capsule shell

Brilliant blue

Gelatine

Quinoline yellow

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Store in a dry place.

Protect from light.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVdC and printed aluminium foil blister strips containing 10 or 20 capsules packed in an outer carton containing 20, 100 or 140 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

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, G/Floor

22 Karee Street

Centurion 0157

8. REGISTRATION NUMBER

A39/2.9/0415

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 February 2006

10. DATE OF REVISION OF THE TEXT

13 April 2023