Professional information for TRAMAZAC CO 37,5

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

TRAMAZAC CO 37,5, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 37,5 mg tramadol (as tramadol hydrochloride) and 325 mg paracetamol.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White coloured, capsule shaped, bevel edged, biconvex film-coated tablets debossed with “334” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRAMAZAC CO 37,5 is indicated for the management of moderate to moderately severe pain in adults.

TRAMAZAC CO 37,5 is not recommended for minor pain that may be treated adequately through lesser means.

4.2 Posology and method of administration

Posology

To be used in adults and children over 16 years of age.

DO NOT EXCEED THE RECOMMENDED DOSE.

For the management of pain, the recommended maximum single dose of TRAMAZAC CO 37,5 is 1 or 2 tablets every 4 to 6 hours as needed for pain relief, up to a maximum of 8 tablets per day. The lowest effective dose should be used for the shortest period of time.

A titration period of several days with gradual dose increases at the initiation of TRAMAZAC CO 37,5 therapy may be beneficial for some patients. Clinical studies with tramadol in patients with moderate to moderately severe chronic pain indicate that the tolerability of tramadol can be improved by starting tramadol at a low dose with gradual upward dose titration to reach doses that provide sufficient pain relief.

Special populations

Elderly patients (65 years of age and older)

No overall differences regarding safety or pharmacokinetics were noted between subjects ≥ 65 years of age and younger subjects.

Renal impairment

In patients with creatinine clearance < 30 mL/min, the dosing interval of TRAMAZAC CO 37,5 should be increased not to exceed 2 tablets every 12 hours.

Hepatic impairment

The use of TRAMAZAC CO 37,5 in patients with moderate to severe hepatic impairment is contraindicated.

Paediatric population

Children below 16 years of age

The use of TRAMAZAC CO 37,5 is contraindicated in children below 12 years of age (see section

4.3).

The safety and effectiveness of TRAMAZAC CO 37,5 in children aged 12 to below 16 years of age have not been established (see sections 4.3 and 4.4).

Method of administration

TRAMAZAC CO 37,5 is for oral administration.

Tablets must be swallowed whole, with a sufficient quantity of liquid and must not be broken or chewed.

TRAMAZAC CO 37,5 can be administered without regard to food.

4.3 Contraindications

- TRAMAZAC CO 37,5 is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol, other opioids such as codeine or to any of the excipients listed in section 6.1.
- Acute intoxication with alcohol, hypnotics, centrally acting analgesics, other opioids or psychotropic medicines.
- Moderate to severe hepatic impairment.
- TRAMAZAC CO 37,5 should not be administered to patients who are receiving monoamine oxidase inhibitors (MAOIs) or within two weeks of their withdrawal (see section 4.5).
- Narcotic withdrawal treatment.
- Cyanosis, excessive bronchial secretions, or any respiratory depression.
- Head injury or cerebral disease, with or without increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.
- Epilepsy or seizures of any cause (see section 4.4).
- Children younger than 12 years of age.
- Children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

4.4 Special warnings and precautions for use

TRAMAZAC CO 37,5 contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

Seizures

TRAMAZAC CO 37,5 should not be used in patients with epilepsy, a history of epilepsy or those susceptible to seizures (see section 4.3).

Seizures have been reported in patients receiving TRAMAZAC CO 37,5 at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients concomitantly taking tricyclic antidepressants or other tricyclic compounds such as selective serotonin reuptake inhibitors (SSRIs), opioids, neuroleptics and other medicines that may reduce the seizure threshold (see section 4.5).

The risk of seizures may also be increased in patients with a recognised risk for seizures, such as drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramadol overdose.

Anaphylactic reactions

Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and therefore should not take TRAMAZAC CO 37,5 (see section 4.3).

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol.

Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol-containing medicines. If a patient develops SCARs, treatment with TRAMAZAC CO 37,5 must immediately be discontinued and appropriate treatment instituted.

Central nervous system (CNS) depressants

Concomitant use of TRAMAZAC CO 37,5 and sedating medicines, such as benzodiazepines or related medicines, may result in sedation, respiratory depression, coma and death. The use of TRAMAZAC CO 37,5 concurrently with other central nervous system depressants, including alcohol, may cause additive CNS depressant 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 CO 37,5 concomitantly with sedating medicines, the lowest effective dose of TRAMAZAC CO 37,5 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).

TRAMAZAC CO 37,5 should be used with caution in patients with biliary tract disorders, a reduced level of consciousness for unknown reasons or who are in a state of shock.

Sleep-related breathing disorders

Opioids, such as TRAMAZAC CO 37,5, may cause sleep-related breathing disorders, including central sleep apnoea (CSA) and sleep-related hypoxaemia. Opioid use increases the risk of CSA

in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of new sleep apnoea or a worsening of existing sleep apnoea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids.

Serotonin syndrome

TRAMAZAC CO 37,5 alone or in combination with other serotonergic medicines, including SSRIs, 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.

Medicine dependence, tolerance and potential for abuse

For all patients, prolonged use of TRAMAZAC CO 37,5 may lead to medicine 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. TRAMAZAC CO 37,5 can reinstate dependence in patients that have previously used or were dependent on opioids. In patients with opioid dependence, treatment with TRAMAZAC CO 37,5 is not recommended.

A comprehensive patient history should be taken to document concomitant medicines, including over-the-counter medicines and medicines obtained online, 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 TRAMAZAC CO 37,5 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.

TRAMAZAC CO 37,5 should not be given to patients who are suicidal or prone to addiction.

Withdrawal

Prior to starting treatment, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with TRAMAZAC CO 37,5.

Medicine 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, panic attacks, hallucinations, paraesthesia, tinnitus, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Renal or hepatic impairment

Dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should only take paracetamol-containing products under medical supervision.

TRAMAZAC CO 37,5 has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of TRAMAZAC CO 37,5 be increased not to exceed 2 tablets every 12 hours (see section 4.2).
In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), TRAMAZAC CO 37,5 is not recommended.

In patients with moderate to severe hepatic impairment, TRAMAZAC CO 37,5 should not be used (see section 4.3).

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy, such as TRAMAZAC CO 37,5, presents with increased pain. This may 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 the dose.

CYP2D6 metabolism

Tramadol, as in TRAMAZAC CO 37,5, 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. Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol to its active metabolite, mono-*O*-desmethyltramadol (M1), more rapidly and completely than other patients. This rapid conversion may result in higher than expected serum M1 levels, which could lead to an increased risk of opioid toxicity. Alternative medication, dose reduction and/or increased monitoring for signs of tramadol toxicity is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

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.

Respiratory disorders

TRAMAZAC CO 37,5 should be used with caution in patients with respiratory disorders.

Adrenal insufficiency

Opioid analgesics, such as TRAMAZAC CO 37,5, 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 CO 37,5, 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 CO 37,5 and appropriate treatment (e.g. fluid restriction). During TRAMAZAC CO 37,5 treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Other conditions

TRAMAZAC CO 37,5 should be used with caution in patients who suffer from emotional disturbance or depression.

General

The recommended dose of TRAMAZAC CO 37,5 should not be exceeded.
TRAMAZAC CO 37,5 should not be used with any other paracetamol- or tramadol-containing products.

Paediatric population

Children under 12 years

TRAMAZAC CO 37,5 is not suitable for children under the age of 12 years (see sections 4.2 and 4.3).

Post-operative use in children

TRAMAZAC CO 37,5 should not be given post-operatively to children (under 18 years of age) with obstructive sleep apnoea after tonsillectomy and/or adenoidectomy 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 CO 37,5 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. These factors may worsen symptoms of opioid toxicity.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors (MAOIs)

The concomitant use of TRAMAZAC CO 37,5 with MAOIs, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see section 4.3). MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g. respiratory depression, coma) (see section 4.4).

Central nervous system (CNS) depressants

The concomitant administration of TRAMAZAC CO 37,5 with other CNS depressants, including alcohol and anaesthetics, may potentiate the CNS depressant effects (see section 4.4).

The concomitant use of opioids, such as TRAMAZAC CO 37,5, 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 of TRAMAZAC CO 37,5 and the duration of concomitant use should be limited (see section 4.4).

Serotonergic medicines

Concomitant therapeutic use of TRAMAZAC CO 37,5 and serotonergic medicines, such as lithium, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAOIs (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8) and may increase the risk of seizures. TRAMAZAC CO 37,5 should be discontinued if serotonin syndrome is suspected.

Seizure threshold-lowering medicines

TRAMAZAC CO 37,5 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 bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions (see section 4.4).

Anticoagulants

As medically appropriate, periodic evaluation of prothrombin time should be performed when TRAMAZAC CO 37,5 and anticoagulants, such as warfarin, are administered concurrently due to reports of increased international normalised ratio (INR). The dosage of warfarin should be adjusted as needed.

TRAMAZAC CO 37,5 may produce hypoprothrombinaemia when administered with warfarin-like medicines.

CYP2D6 and CYP3A4 inhibitors

CYP2D6 inhibitors (such as amitriptyline, fluoxetine, quinidine, paroxetine) and CYP3A4 inhibitors (such as ketoconazole and erythromycin) may inhibit the metabolism of tramadol.

The concomitant use of TRAMAZAC CO 37,5 and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of TRAMAZAC CO 37,5 is achieved.

The concomitant use of TRAMAZAC CO 37,5 and an inhibitor of CYP3A4 can increase the plasma concentration of tramadol and may result in increased metabolism via CYP2D6 and higher levels of M1.

CYP3A4 inducers

CYP3A4 inducers (such as rifampicin, phenytoin) may result in an increased rate of tramadol metabolism, decreasing the plasma concentration and reducing the therapeutic effect of

TRAMAZAC CO 37,5.

Carbamazepine

Administration of TRAMAZAC CO 37,5 with carbamazepine (enzyme inducer) may reduce the serum concentrations, lower the analgesic effect and shorten the duration of action of TRAMAZAC CO 37,5.

Ondansetron

The antiemetic 5-HT3 antagonist, ondansetron, may increase the requirement of TRAMAZAC CO 37,5 in patients with post-operative pain.

Cimetidine

Clinically insignificant changes in serum concentration are seen with concomitant administration with cimetidine. Therefore, patients receiving chronic therapy with cimetidine should not alter the dosage regimen of TRAMAZAC CO 37,5 treatment.

Diflunisal

Concomitant administration of diflunisal and paracetamol caused a 50 % increase in paracetamol plasma levels. Therefore, during concomitant administration of TRAMAZAC CO 37,5 and diflunisal, patients should be monitored carefully.

Other medicines

The absorption of paracetamol, as in TRAMAZAC CO 37,5, may be enhanced by metoclopramide and reduced by colestyramine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use in pregnancy has not been established. Tramadol has been shown to cross the placenta and therefore should not be used by pregnant women.

Breastfeeding

Safe use in lactation has not been established. Tramadol may appear in breast milk and therefore should not be used by lactating mothers.

4.7 Effects on ability to drive and use machines

TRAMAZAC CO 37,5 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 (see section 4.5). Caution is advised before driving a vehicle or operating machinery until the effects of TRAMAZAC CO 37,5 are known.

4.8 Undesirable effects

Summary of the safety profile

The most frequent side effects during treatment with TRAMAZAC CO 37,5 are nausea, dizziness and somnolence, which were observed in more than 10 % of the patients.

List of adverse reactions

The following adverse reactions have been reported with tramadol and paracetamol combination such as TRAMAZAC CO 37,5:

Blood and lymphatic system disorders

Less frequent: anaemia

Metabolism and nutrition disorders

Frequent: anorexia

Less frequent: weight decrease

Frequency unknown: hypoglycaemia

Psychiatric disorders

Frequent:	anxiety, confusion, euphoria, sleep disorders (insomnia), nervousness, altered mood
Less frequent:	depersonalisation, depression, medicine dependence (see section 4.4), emotional lability, hallucinations, impotence, nightmares, abnormal thinking, delirium

Nervous system disorders

Frequent:	dizziness, somnolence, headache, tremors
Less frequent:	ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, amnesia, stupor, syncope, speech disorders

Eye disorders

Less frequent:	abnormal/blurred vision, miosis, mydriasis

Ear and labyrinth disorders

Less frequent:	tinnitus, vertigo

Cardiac disorders

Less frequent:	dysrhythmia, palpitations, tachycardia

Vascular disorders

Less frequent:	hypertension, aggravated hypertension, hypotension, hot flushes

Respiratory, thoracic and mediastinal disorders

Less frequent:	dyspnoea
Frequency unknown:	hiccups

Gastrointestinal disorders

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

Less frequent: dysphagia, melaena, tongue oedema

Hepatobiliary disorders

Less frequent: liver test abnormalities (transaminases increased), hepatitis

Skin and subcutaneous tissue disorders

Frequent: pruritus, rash, hyperhidrosis

Less frequent: urticaria

Renal and urinary disorders

Less frequent: albuminuria, micturition disorders (dysuria, oliguria and urinary retention)

General disorders and administration site conditions

Frequent: asthenia, fatigue

Less frequent: chest pain, rigors (chills), medicine withdrawal syndrome.

Post-marketing experience

Immune system disorders

Fixed drug eruption (FDE).

Metabolism and nutrition disorders

Hyponatraemia/syndrome of inappropriate antidiuretic hormone (SIADH).

Description of selected adverse reactions

Hyponatraemia:

Hyponatraemia and/or SIADH may occur with TRAMAZAC CO 37,5, usually in patients with

predisposing risk factors, such as elderly patients or those using concomitant medicines that may cause hyponatraemia (see section 4.4).

The following adverse reactions have been reported for tramadol in clinical studies and post-marketing experience:

Blood and lymphatic system disorders

Frequency unknown: alteration of warfarin effect, including elevation of prothrombin times

Immune system disorders

Less frequent: allergic reactions (including anaphylaxis, urticaria, wheezing and Stevens-Johnson syndrome/toxic epidermal necrolysis)

Metabolism and nutrition disorders

Less frequent: changes in appetite

Frequency unknown: hypoglycaemia, hyponatraemia/syndrome of inappropriate antidiuretic hormone (SIADH)

Psychiatric disorders

Frequency unknown: suicidal tendency, restlessness, changes in activity (usually suppression, occasionally increase), changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders), changes in mood (usually euphoric mood, occasionally dysphoria), delirium

Nervous system disorders

Less frequent: cognitive dysfunction, difficulty concentrating

Frequency unknown: dysphoria, serotonin syndrome (especially at high doses or when given with other serotonergic medicines), raised intracranial pressure

Cardiac disorders

Frequency unknown: bradycardia, myocardial ischaemia

Vascular disorders

Less frequent: orthostatic hypotension

Frequency unknown: vasodilation, cardiovascular collapse

Respiratory, thoracic and mediastinal disorders

Less frequent: lung oedema, respiratory depression

Frequency unknown: worsening of asthma

Gastrointestinal disorders

Frequency unknown: gastrointestinal bleeding

Skin and subcutaneous tissue disorders

Frequency unknown: contact dermatitis

Musculoskeletal and connective tissue disorders

Less frequent: muscle weakness

Frequency unknown: muscle rigidity (after high doses), movement disorders

Renal and urinary disorders

Frequency unknown: ureteric or biliary spasm

Reproductive system and breast disorders

Frequency unknown: decreased libido

General disorders and administration site conditions

Less frequent: medicine withdrawal syndrome, hypothermia

Investigations

Less frequent: elevated creatinine and prothrombin levels.

Post-marketing experience

Gastrointestinal disorders

Increased risk of abdominal pain, including pancreatitis.

The following adverse reactions have been reported for paracetamol in clinical studies and post-marketing experience:

Blood and lymphatic system disorders

Less frequent: agranulocytosis, thrombocytopenia, pancytopenia, leucopenia, neutropenia

Immune system disorders

Less frequent: allergic reactions (primarily skin rash)

Frequency unknown: angioedema

Metabolism and nutrition disorders

Frequency unknown: pyroglutamic aciduria, high anion gap metabolic acidosis (HAGMA)

Skin and subcutaneous tissue disorders

Frequency unknown: toxic epidermal necrolysis

Renal and urinary disorders

Frequency unknown: nephropathy

Investigations

Less frequent: hypoprothrombinaemia.

Post-marketing experience

Skin and subcutaneous disorders

*S*evere cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TRAMAZAC CO 37,5 is important. It allows continued monitoring of the benefit/risk balance of TRAMAZAC CO 37,5. 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

Accidental ingestion

Accidental ingestion of tramadol can result in respiratory depression and seizures due to an overdose with tramadol. Respiratory depression and seizures have been reported in a child following ingestion of a single tablet.

Fatalities due to tramadol overdose have also been reported.

Signs and symptoms

TRAMAZAC CO 37,5 is a fixed combination of active substances. Clinical presentation of overdosage may include symptoms of either tramadol or paracetamol toxicity, or both.

Tramadol

The symptoms of tramadol overdosage may include miosis, vomiting, fast heartbeat, consciousness disorders up to coma, cardiovascular collapse, cardiac arrest, death, respiratory depression including respiratory arrest and/or seizures. In addition, cases of QT prolongation have been reported during overdose.

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

Paracetamol

Symptoms of paracetamol overdosage in the first 24 hours include gastrointestinal abnormality, abdominal pain, pallor, nausea, vomiting, malaise, anorexia and diaphoresis. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Paracetamol in massive overdosage may cause hepatic toxicity. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac dysrhythmias and pancreatitis have been reported.

Treatment

Tramadol

A single or multiple overdose with TRAMAZAC CO 37,5 may be a potentially lethal polymedication overdose, and appropriate expert consultation, if available, is recommended.

While naloxone will reverse some, but not all symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Based on experience with tramadol,

haemodialysis is not expected to be helpful in an overdose because it removes less than 7 % of the administered dose in a 4-hour dialysis period.

Primary attention should be given to maintaining adequate ventilation and circulatory functions along with general supportive treatment.

Restlessness and convulsions can be treated symptomatically with benzodiazepines and/or barbiturates.

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.
Liver damage may become apparent 12 – 48 hours or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time / increased INR.

Treatment of paracetamol overdose

It is recommended that any adult person who has ingested 5 – 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients

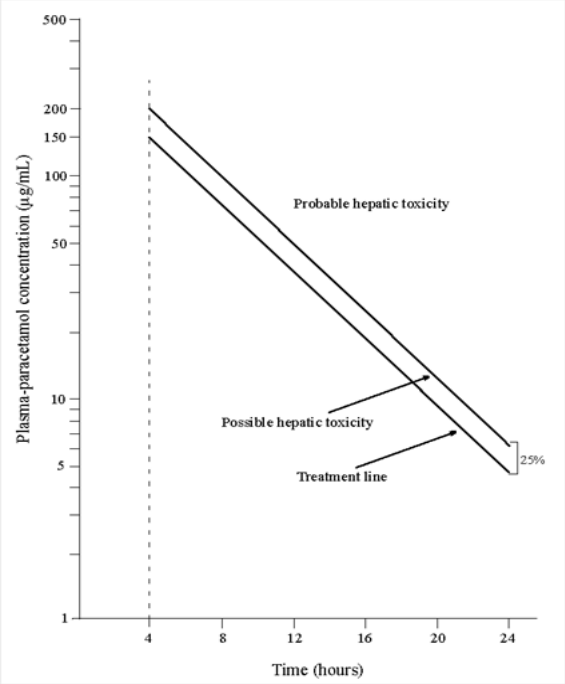
who are stuporous or comatose, endotracheal intubation should precede gastric lavage in order to avoid aspiration.

***N*-acetylcysteine** should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. Administration should not be delayed while awaiting the results of the plasma assay.

IV: An initial dose of 150 mg/kg *N*-acetylcysteine in 200 mL dextrose 5 % *m/v* injection should be given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL dextrose 5 % *m/v* injection over the next 4 hours, and then 100 mg/kg in 1 000 mL dextrose 5 % *m/v* injection over the next 16 hours. **The intravenous fluid volumes should be modified for children**. Sodium chloride 0,9 % *m/v* injection may be used where dextrose 5 % *m/v* injection is unsuitable.

Orally: Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every 4 hours for 17 doses.

A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels done before 4 hours, unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with *N*-acetylcysteine, can be identified according to their plasma paracetamol level.
The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



A semi-logarithmic plot of plasma-paracetamol concentration against hours after ingestion (adapted from Rumack BH, Matthew HJ. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55: 871–6).

Those whose plasma paracetamol levels are above the “Treatment line”, should continue *N*-acetylcysteine treatment with 100 mg/kg intravenously over 16 hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “Possible hepatic toxicity” line. Prothrombin index correlates best with survival.

All patients with significant ingestion of paracetamol should be monitored for at least 96 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other analgesics.

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics, tramadol and paracetamol.

ATC code: N02AJ13.

Mechanism of action

Tramadol is a synthetic analgesic compound which acts centrally. The analgesic profile of tramadol can be contributed to the binding of the parent and *O*-demethylated (M1) metabolite to μ-opioid receptors as well as the weak inhibition of neuronal uptake norepinephrine (noradrenaline) and serotonin. Paracetamol also has centrally acting analgesic effects.

5.2 Pharmacokinetic properties

Absorption

After oral administration tramadol is well absorbed, and peak activity is reached within 2 to 3 hours. The mean absolute bioavailability of 100 mg tramadol (single dose) is about 75 %. Bioavailability can increase to approximately 90 % with multiple dosing. Peak plasma concentration of paracetamol after oral administration is within 1 hour. The absorption of paracetamol is not affected by the co-administration of tramadol.

Distribution

Tramadol has a high tissue affinity. Plasma protein binding is 20 %. Paracetamol appears to be widely distributed throughout most body tissues, except fat. Its apparent volume of distribution is about 0,9 L/kg. A relatively small portion of paracetamol binds to plasma proteins.

Biotransformation

Tramadol and paracetamol are both extensively metabolised by the liver. Tramadol is metabolised by a number of pathways including the cytochrome P450 isoenzymes, CYP3A4 and CYP2D6, as well as by conjugation. Paracetamol is metabolised from the body primarily by formation of glucuronide and sulphate conjugates in a dose-dependent manner.

Elimination

Approximately 30 % of tramadol is excreted unchanged in the urine, and the rest along with the metabolites are eliminated primarily by the kidneys. Plasma elimination half-lives of tramadol and

the M1 metabolite are approximately 6 and 7 hours, respectively. The half-life of paracetamol in adults is about 2 to 3 hours. Less than 9 % is excreted unchanged in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Magnesium stearate

Maize starch

Microcrystalline cellulose

Pregelatinised starch

Sodium starch glycolate.

Tablet coating

Opadry White 03F58991 (containing hypromellose, macrogol, talc and 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.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

White opaque PVDC/PVC/silver aluminium blister strips, containing 10 tablets each. Each outer carton contains 3 or 6 blister strips.

Pack sizes: 30 or 60 tablets.

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, Ground Floor

22 Karee Street

Centurion 0157

8. REGISTRATION NUMBER

45/2.9/0303

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

20 June 2013

10. DATE OF REVISION OF THE TEXT

01 March 2024