1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

TRAMASPEN CO 37,5 mg/325 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRAMASPEN CO:

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

Sugar free.

Contains 0,122 mmol to 0,182 mmol of sodium

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

TRAMASPEN CO is a yellow coloured, elongated, film-coated tablet with “325” debossed on the one side and “37,5” debossed on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TRAMASPEN CO is indicated for the management of moderate to moderately severe pain in adults.

TRAMASPEN CO 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.

Adults

For the management of pain, the recommended dose of TRAMASPEN CO is 1 or 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

As with all analgesic medicines, a titration period of several days with gradual dose increases at the initiation of TRAMASPEN CO therapy may be beneficial for some patients.

Clinical studies with tramadol in patients with moderate to moderately severe chronic pain indicated that the tolerability of tramadol can be improved by starting at a lower dose with gradual upward titration to reach doses that provide sufficient pain relief.

Special populations

Renal impairment

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

Method of administration

For Oral use

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

4.3. Contraindications

- TRAMASPEN CO is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol, or any of the other ingredients mentioned in section 6.1 or other opioids such as codeine.
- TRAMASPEN CO is also contraindicated in cases of severe liver function impairment and in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines.
- TRAMASPEN CO should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.
- TRAMASPEN CO must not be used for narcotic withdrawal treatment.
- TRAMASPEN CO should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions.
- TRAMASPEN CO should not be given to patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.
- TRAMASPEN CO is contraindicated in epilepsy not controlled by treatment.

4.4. Special warnings and precautions for use

The maximum dose of 8 tablets of TRAMASPEN CO should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over thecounter) or tramadol hydrochloride containing products concurrently without the advice of a medical practitioner. (See section 4.9)

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.

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

Tramadol as contained in TRAMASPEN CO may only be taken with special care in opioid dependence, reduced level of consciousness of uncertain origin, disorders of the respiratory function and increased intracranial pressure.

Seizures:

Seizures have been reported in patients receiving tramadol as contained in TRAMASPEN CO at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g. promethazine, selective serotonin re- uptake inhibitors, MAO-inhibitors and neuroleptics. 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 as contained in TRAMASPEN CO overdose. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with tramadol as contained in TRAMASPEN CO.

CYP2D6 ultra-rapid metabolism of tramadol:

Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol as contained in TRAMASPEN CO to its active metabolite(M1) more rapidly and completely than other patients. This rapid conversion may lead to higher than expected serum M1 levels which could lead to an increased risk of respiratory depression. Alternative medicine, dose reduction and/or increased monitoring for signs of tramadol as contained in TRAMASPEN CO overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Drug abuse and dependence

Tramadol as contained in TRAMASPEN CO has a dependence potential and tolerance, psychic and physical dependence of the morphine type (μ opioid) may develop with long-term use. The medicine has been associated with craving, drug-seeking behaviour and tolerance development. Cases of abuse and dependence on tramadol as contained

in TRAMASPEN CO have been reported. Tramadol as contained in TRAMASPEN CO should not be used in opioid-dependent patients. Tramadol as contained in TRAMASPEN CO 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 as contained in TRAMASPEN CO is not recommended.

Withdrawal:

Withdrawal symptoms may occur if TRAMASPEN CO is discontinued abruptly. Panic attacks,severe anxiety, hallucinations, paraesthesia, tinnitus, and unusual CNS symptoms have also been reported with abrupt discontinuation of tramadol hydrochloride as contained in TRAMASPEN CO. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medicine.

Serious skin reactions:

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens- Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving paracetamol as contained in TRAMASPEN CO. Patients should be informed about the signs of serious skin reactions, and use of TRAMASPEN CO should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

General precautions

Do not co-administer TRAMASPEN CO with other tramadol or paracetamol containing medicines.

Use with alcohol

TRAMASPEN CO should not be taken with alcohol containing beverages.

Use with CNS depressants:

The administration of TRAMASPEN CO concurrently with central nervous system (CNS) depressants such as alcohol, opioids, anaesthetic medicines, phenothiazines, tranquilisers or sedative hypnotics is likely to intensify and prolong CNS effects.

Use in renal disease:

TRAMASPEN CO should be used with caution in patients with impaired renal function and in patients prone to convulsive disorders or in shock.

Hyponatraemia:

Hyponatraemia has been reported with the use of TRAMASPEN CO usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medicines 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 TRAMASPEN CO and appropriate treatment (e.g. fluid restriction). During TRAMASPEN CO treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

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.

4.5. Interaction with other medicines and other forms of interaction

Concomitant use is contraindicated with:

Monoamine oxidase (MAO) Inhibitors

- Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol as contained in TRAMASPEN CO.

Concomitant use is not recommended with:

Alcohol

- Alcohol increases the sedative effect of opioid analgesics. The effect on alertness can make driving of vehicles and the use of machines dangerous. Avoid intake of alcoholic drinks and of medicinal products containing alcohol.

Carbamazepine and other enzyme inducers

- Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol as contained in TRAMASPEN CO.

Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)

- Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

Concomitant use which needs to be taken into consideration:

- Tramadol as contained in TRAMASPEN CO can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and seizure threshold- lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.
- Concomitant therapeutic use of tramadol as contained in TRAMASPEN CO and serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs) serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.2), 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 or ocular clonus.

Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

- Other opioid derivatives (including antitussive medicines and substitutive treatments) increased risk of respiratory depression which can be fatal in cases of overdose.

- Other central nervous system depressants, such as other opioid derivatives (including antitussive medicines and substitutive treatments), other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive medicines, thalidomide and baclofen.

These medicines can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

- Sedating medicinal products such as benzodiazepines or related substances:
    - The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dose and duration of the concomitant use should be limited (see section 4.4).
- As medically appropriate, periodic evaluation of prothrombin time should be performed when TRAMASPEN CO and warfarin -like compounds are administered concurrently due to reports of increased INR.

Post- marketing surveillance of tramadol as contained in TRAMASPEN CO has revealed rare reports of digoxin toxicity. Concomitant administration of diflunisal and paracetamol as contained in TRAMASPEN CO produces a 50 % increase in paracetamol plasma levels in normal volunteers. TRAMASPEN CO should be used cautiously and patients should be monitored carefully.

Concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine and amitriptyline may inhibit the metabolism of TRAMASPEN CO.

Ondansetron increased the requirement of tramadol as contained in TRAMASPEN CO in patients with post-operative pain.

4.6. Fertility, pregnancy and lactation

Safe use in pregnancy and lactation has not been established. TRAMASPEN CO is not recommended for pregnant mothers because tramadol as contained in TRAMASPEN CO has been shown to cross the placenta.

Fertility

Post marketing surveillance does not suggest an effect of tramadol as contained in TRAMASPEN CO on fertility.

4.7. Effects on ability to drive and use machines

Tramadol as contained in TRAMASPEN CO may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

TRAMASPEN CO can impair cognitive function and can affect a patient's ability to drive safely.When prescribing this medicine, patients should be told that TRAMASPEN CO is likely to affect your ability to drive. Patients should be told to not drive until they know how TRAMASPEN CO affects them.

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Metabolism and nutrition disorders			Hypoglycaemia
Psychiatric disorders	Confusional state, mood altered, anxiety, nervousness, euphoric mood), sleep disorders,	Depression, hallucinations, depersonalisation , nightmares, delirium, drug dependence, drug abuse, impotence.	

	anorexia		
Nervous system disorders	Dizziness, somnolence, headache, tremor.	Involuntary muscular contractions, paraesthesia, amnesia, ataxia, convulsions, syncope, speech disorders	
Eye disorders		vision blurred, miosis, mydriasis	
Ear and labyrinth disorders		Tinnitus	
Blood disorders		Anaemia	
Cardiac disorders		Palpitations, tachycardia, dysrhythmia	
Gastrointestinal disorders	Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence	Dysphagia , melaena	
General disorders and administration site conditions		Chills, chest pain, asthenia,fatigue, decreased weight	
Investigations:		Tranaminases increased	
Renal and urinary disorders		Albuminuria, micturition disorders(dysuria and urinary retention), oliguria	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	
Skin and subcutaneous tissuedisorders	Hyperhidrosis , pruritus	Dermal reactions (e.g. rash,urticaria).	
Vascular disorders:		Hypertension, aggravated hypertension, hot flush, hypotension	

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or paracetamol as contained in TRAMASPEN CO cannot be excluded:

Tramadol

- Postural hypotension, bradycardia, collapse (tramadol).
- Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
- Cases of less frequent: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioedema) and anaphylaxis.
- Less frequent: changes in appetite, motor weakness and respiratory depression.
- Psychic side effects may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood, (usually euphoric mood occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders).
- Worsening of asthma has been reported though a causal relationship has not been established.
- Rare side effect: Increased risk of abdominal pain, including pancreatitis.
- 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 been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Paracetamol

- Hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis.
- There have been several reports that suggest that paracetamol may produce hypoprothrombinaemia when administered with warfarin like compounds. In other studies, prothrombin time did not change.
- Cases of serious skin reactions have been reported.

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 providers are asked to report any suspected adverse reactions to:

SAHPRA: via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

The clinical presentation of overdosage may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both.

Tramadol

The initial symptoms of tramadol overdosage may include respiratory depression and/or seizures.

Primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all symptoms caused by overdosage, the risk of seizures is also increased with naloxone administration.

Treatment of restlessness and / or convulsions is symptomatic and supportive (benzodiazepines / barbiturates). Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with TRAMASPEN CO with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

Paracetamol

Prompt treatment is essential**.** In the event of an overdosage, consult a medical practitioner immediately, or take the person directly to a hospital. A delay in starting treatment may mean that 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 to 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. Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning, do not reflect the potential seriousness of the overdosage. Liver damage may become apparent 12 to 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

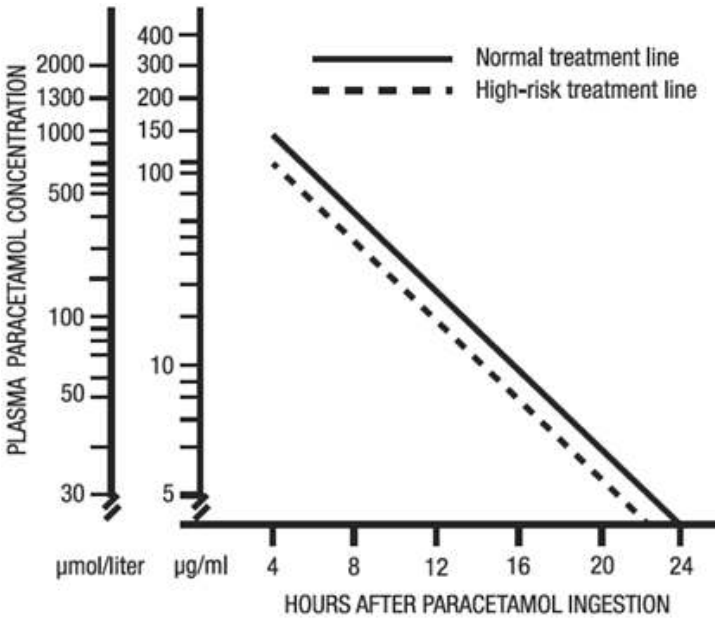
time. Liver damage may lead to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Treatment for paracetamol overdosage:

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. An initial dose of 150 mg/kg N-acetylcysteine in 200 mL dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL dextrose injection over the next four hours, and then 100 mg/kg in 1 000 mL dextrose injection over the next sixteen hours.

The volume of intravenous fluid should be modified for children.

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 four hours for seventeen doses. A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours 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 overdose nomogram.



Those whose plasma paracetamol levels are above the “normal treatment line” , should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery.Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.

Monitor all patients with significant ingestions for at least ninety six 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

Tramadol is a centrally acting synthetic analgesic compound whose analgesic profile can be attributed to the binding of parent and O-demethylated (M1) metabolite to µ-

opioid receptors as well as the weak inhibition of neuronal re-uptake of noradrenaline and serotonin. Paracetamol also has centrally acting analgesic effects.

5.2. Pharmacokinetic properties

Absorption

Tramadol is well absorbed after oral administration, reaching peak activity in 2 to 3 hours. The mean absolute bioavailability of a single 100 mg oral dose is approximately 75 %, increasing to approximately 90 % with multiple dosing. Oral absorption of paracetamol following administration of TRAMASPEN CO gives a peak plasma concentration of paracetamol within one hour and is not affected by co-administration with tramadol.

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}$=203 ± 40 L).

It has a plasma protein binding of about 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 (~20 %) ofparacetamol is bound to plasma proteins.

Biotransformation

Tramadol and paracetamol are both extensively metabolised in the liver.

Elimination

Approximately 30 % of tramadol is excreted unchanged in the urine. Tramadol and its metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of tramadol and its M1 metabolite are approximately 6 and 7 hours respectively.

Paracetamol is eliminated from the body primarily by formation of glucuronide and sulphate conjugates in a dose-dependent manner. The half-life of paracetamol is about 2 - 3 hours in adults. Less than 9 % of paracetamol is excreted unchanged in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hypromellose, iron oxide yellow, macrogol, magnesium stearate, microcrystalline cellulose, polysorbate, pregelatinised starch, sodium starch glycolate, titanium dioxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

6.5. Nature and contents of container

Blister strip of white opaque PVC/PVDC film with aluminium foil lidding containing 10 tablets. 60 tablets are packed in an outer cardboard carton.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

44/2.9/0880

9. DATE OF FIRST AUTHORISATION

22 February 2022

10. DATE OF REVISION OF TEXT

24 August 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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