# PACKAGE INSERT

## SCHEDULING STATUS

Schedule 5

## PROPRIETARY NAME AND DOSAGE FORM

TRAMACET® Tablets

## COMPOSITION

Each tablet contains 37,5 mg tramadol hydrochloride and 325 mg paracetamol as the active ingredients.

Inactive ingredients include the following: carnauba wax, magnesium stearate, OPADRY® Light yellow, powdered cellulose, pregelatinised starch, purified water, sodium starch glycolate, and starch.

## PHARMACOLOGICAL CLASSIFICATION

A.2.9. Other analgesics

## PHARMACOLOGICAL ACTION

### Pharmacodynamic properties

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.

### 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 TRAMACET gives a peak plasma concentration of paracetamol within one hour and is not affected by co-administration with tramadol.

**Metabolism**

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 sulfate 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.

## INDICATIONS

TRAMACET is indicated for the management of moderate to moderately-severe pain in adults.

TRAMACET is not recommended for minor pain that may be treated adequately through lesser means.

## CONTRAINDICATIONS

TRAMACET is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol or other opioids such as codeine.

It is also contraindicated in cases of severe liver function impairment and in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines.

It should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal.

TRAMACET must not be used for narcotic withdrawal treatment.

TRAMACET should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions.

TRAMACET should not be given to patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.

**WARNINGS AND SPECIAL PRECAUTIONS**

**This product 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.**

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

Tramadol 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 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 overdose. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with tramadol.

**CYP2D6 ultra-rapid metabolism of tramadol:**

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

**Drug Abuse and Dependence:**

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

**Withdrawal:**

Withdrawal symptoms may occur if TRAMACET is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paraethesia, tinnitus, and unusual CNS symptoms have also been reported with abrupt discontinuation of tramadol hydrochloride. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

**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. Patients should be informed about the signs of serious skin reactions, and use of TRAMACET should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

**Precautions – general:**

Do not co-administer TRAMACET with other tramadol or paracetamol containing products.

**Use with alcohol:**

TRAMACET should not be taken with alcohol containing beverages.

**Use with CNS depressants:**

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

**Use in renal disease:**

TRAMACET 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 TRAMACET, 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 TRAMACET and appropriate treatment (e.g. fluid restriction). During TRAMACET treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

**Effects on ability to drive or operate machinery:**

Tramadol may affect reactions to the extent that driving ability and the ability to operate machinery may be impaired. This applies particularly in conjunction with other psychotropic medicines including alcohol.

**INTERACTIONS**

Concomitant administration of TRAMACET and carbamazepine may cause significantly decreased tramadol and M1 concentrations. Patients receiving carbamazepine may have significantly reduced analgesic effect from the tramadol component of TRAMACET.

Concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine and amitriptyline could result in some inhibition of the metabolism of tramadol.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore, no alteration of the TRAMACET dosage regimen is recommended for patients receiving chronic cimetidine therapy.

TRAMACET must not be combined with a MAO-inhibitor, or within 14 days of discontinuation of it, as potentiation of serotonergic and noradrenergic effects may result.

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and rare alterations of warfarin effect including elevation of prothrombin times.

Periodic evaluation of prothrombin time / INR should be performed when TRAMACET is administered concurrently with warfarin like compounds, due to reports of increased prothrombin time / INR in some patients.

Concomitant administration of diflunisal and paracetamol produces a 50 % increase in paracetamol plasma levels in normal volunteers. TRAMACET should be used cautiously and patients should be monitored carefully.

**PREGNANCY AND LACTATION**

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

**DOSAGE AND DIRECTIONS FOR USE**

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 TRAMACET 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 TRAMACET 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.

**Renal impairment**

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

## SIDE EFFECTS

TRAMACET tablets may have side effects. These are classified as follows:

- very common (≥ 1/10)
- common (≥ 1/100, < 1/10)
- uncommon (≥ 1/1 000, < 1/100)
- rare (≥ 1/10 000, < 1/1 000)
- very rare (< 1/10 000, including isolated reports)

The most frequently reported side effects were of the gastrointestinal and central nervous systems.

| SYSTEM ORGAN CLASS | Very common (≥ 1/10) | Common (≥ 1/100, < 1/10) | Uncommon (≥ 1/1 000, < 1/100) |
|---|---|---|---|
| Cardiovascular Disorders | | | Hypertension, aggravated hypertension, hypotension dysrhythmia, palpitation, tachycardia |
| Liver and Biliary System | | | Liver test abnormalities |
| Central and Peripheral Nervous System | Dizziness, somnolence | Headache, tremor | Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo |
| Gastrointestinal System | Nausea | Abdominal pain, constipation, diarrhoea, dyspepsia, flatulence | Dysphagia, melena, tongue oedema |

| | | | |
|---|---|---|---|
| | | dry mouth, vomiting | |
| Hearing and Vestibular Disorders | | | Tinnitus |
| Metabolic and Nutritional Disorders | | | Weight decrease |
| Psychiatric Disorders | | Anorexia, anxiety, confusion, euphoria, insomnia, nervousness | Amnesia, depersonalisation, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, abnormal thinking |
| Red Blood Cell Disorders | | | Anaemia |
| Respiratory System | | | Dyspnoea |
| Urinary System | | | Albuminuria, micturition disorder, oliguria, urinary retention |
| Vision Disorders | | | Abnormal vision |

| | | | |
|---|---|---|---|
| Body as a Whole | | Asthenia, fatigue, hot flushes | Chest pain, rigors, syncope, withdrawal syndrome |
| Skin and Appendages | | Pruritus, rash, increased sweating | |

***Clinically significant adverse experiences previously reported in clinical trials or post-marketing reports with tramadol hydrochloride include:***

Orthostatic hypotension, allergic reactions (including anaphylaxis and urticaria, Stevens Johnson Syndrome/TENS), cognitive dysfunction, suicidal tendency and hepatitis. Reported laboratory abnormalities included elevated creatinine.

Serotonin syndrome (whose symptoms may include fever, excitation, shivering and agitation) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAO inhibitors. Post – marketing experience with the use of tramadol containing products included reports of delirium, miosis, mydriasis, and speech disorder, and reports of movement disorder. Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times. Cases of hypoglycemia have been reported.

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.

***Clinically significant adverse experiences previously reported in clinical trials or post-marketing reports with paracetamol include:***

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to paracetamol are rare and generally controlled by discontinuation of the medicine, and when necessary, symptomatic treatment. There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin like compounds. In other studies, prothrombin time did not change.

**KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT**

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 TRAMACET with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

**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 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 drugs 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 arrhythmias have been reported.

**Treatment for paracetamol overdosage:**

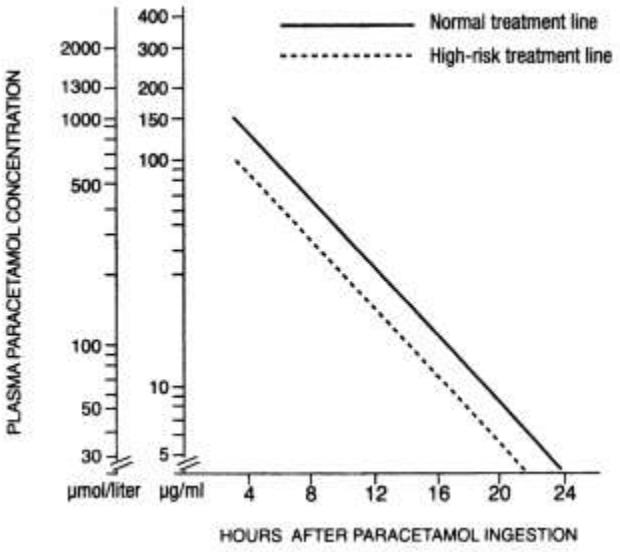
Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 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 stuperose 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. 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 1000 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, 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 normogram below.




Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th Ed.

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.

**IDENTIFICATION**

Light yellow, film-coated capsule-shaped tablet engraved "J-C" on one side and "T/P" on the other.

**PRESENTATION**

Blister packs of 60 tablets.

**STORAGE INSTRUCTIONS**

Store in a cool, dry place, at or below 25 ºC.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBER**

35/2.9/0010

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION**

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## DATE OF PUBLICATION OF THE PACKAGE INSERT

Date on the registration certificate: 07 March 2003.

Date of the most recently revised Package insert as approved by Council: 15 February 2016.