AUSTRALIAN PRODUCT INFORMATION – APO-TRAMADOL/PARACETAMOL 37.5/325 TABLETS (TRAMADOL HYDROCHLORIDE, PARACETAMOL) TABLET

1 NAME OF THE MEDICINE

Tramadol hydrochloride and paracetamol

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Each film-coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol, as the active ingredients.

In addition, each film-coated tablet contains the following inactive ingredients: povidone, pregelatinised maize starch, stearic acid, microcrystalline cellulose, croscarmellose sodium, hypromellose, hyprolose, macrogol 8000, titanium dioxide and iron oxide yellow.

APO-Tramadol/Paracetamol 37.5/325 appears as a yellow, capsule-shaped, biconvex, film-coated tablet with engraving of “APO” on one side and “37.5 - 325” on the other. Each film-coated tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol as the active ingredients.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

APO-Tramadol/Paracetamol 37.5/325 tablets is indicated for the treatment of moderate pain.

4.2 DOSE AND METHOD OF ADMINISTRATION

ADULTS AND ADOLESCENTS (12 years and older)

The dose should be individually adjusted according to intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

An initial dose of two tablets of tramadol/paracetamol tablets (equivalent to 75 mg tramadol hydrochloride and 650 mg paracetamol) is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (film-coated) (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should not be less than 6 hours.

Patients weighing between 37.5 kg and 50 kg should receive a maximum of 6 tramadol/paracetamol tablets daily. Patients weighing less than 37.5 kg should not receive tramadol/paracetamol tablets.

Tramadol/paracetamol tablets should under no circumstances be administered for longer than is strictly necessary (see 4.4-Special warnings and precautions for use). If repeated use or long term treatment with tramadol/paracetamol tablets is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Method of Administration

Oral use

Tramadol/paracetamol tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

4.3 CONTRAINDICATIONS

- hypersensitivity to tramadol, paracetamol or to any other components of the tablet,
- acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs,
- tramadol/paracetamol tablets should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see 4.5-Interactions with other medicines and other forms of interactions),
- in cases of severe hepatocellular insufficiency
- in patients with hepatic failure or decompensated active liver disease,
- epilepsy not controlled by treatment (see 4.4-Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Maximum daily dose

In adults and adolescents 12 years and older, the total dose of 8 tablets of tramadol/paracetamol tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day should not be exceeded. The dosing interval should not be less than six hours. 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 the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.

Tramadol/paracetamol tablets contains tramadol HCl and paracetamol. Paracetamol has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of paracetamol at doses that exceed 4,000 milligrams per day, and often involve more than one paracetamol-containing product.

Use in hepatic impairment

The pharmacokinetics of tramadol/paracetamol tablets have not been studied in patients with hepatic impairment. Tramadol and paracetamol are both extensively metabolised by the liver.

In patients with hepatic impairment the elimination of tramadol is delayed. In these patients prolongation of dosage interval should be carefully considered according to the patient's requirements.

Because of the presence of paracetamol, tramadol/paracetamol tablets should not be used in patients with severe hepatic impairment.

Tramadol HCl:

The relationship between degree of hepatic impairment and half-life of tramadol has not been extensively studied to provide a dosing recommendation for tramadol; instead, an

individual dosing regimen based on the patient's needs is proposed. A dose interval prolongation should be carefully considered.

Paracetamol:

In patients with chronic or active hepatic disease, especially those with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration, the paracetamol dose should not exceed 3 g/day. It is of note that the maximum daily dose of tramadol/paracetamol tablets (8 tablets) is equivalent to 2.6 g paracetamol.

Use in renal impairment

In patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of dosage interval should be carefully considered according to the patient's requirements.

Use in patients with respiratory insufficiency

Tramadol/paracetamol tablets should be administered cautiously in patients at risk of respiratory depression. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result.

Opioid-dependent patients

Tramadol is not recommended as a substitute in opioid-dependent patients. Although tramadol is an opioid-agonist, it cannot suppress opioid withdrawal symptoms. Animal experiments have shown that under certain circumstances the administration of tramadol may provoke a withdrawal syndrome in opioid dependent monkeys.

Because of the difficulty in assessing dependence in patients who have previously received substantial amounts of opioid medications, caution should be used in the administration of tramadol/paracetamol tablets to such patients. In patients with tendency for drug abuse or dependence, treatment with tramadol/paracetamol tablets should only be carried out for short periods under strict medical supervision. Cases of dependence and abuse of tramadol have been reported rarely.

Concomitant use of opioid agonists-antagonists (buprenorphine, pentazocine) is not recommended (see 4.5-Interactions with other medicines and other forms of interactions)

Increased intracranial pressure, head trauma, shock or reduced levels of consciousness

Tramadol/paracetamol tablets should be used with caution in patients with increased intracranial pressure, head injury, shock or a reduced level of consciousness of uncertain origin.

Pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating mental status in these patients if they are receiving tramadol/paracetamol tablets.

Misuse, abuse and diversion

Tramadol has mu-opioid agonist activity. Tramadol/paracetamol tablets, a tramadol-containing product, can be sought by drug abusers and people with addiction disorders and

may be subject to criminal diversion. The possibility of illegal or illicit use should be considered when prescribing or dispensing tramadol/paracetamol tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Misuse or abuse poses a significant risk to the abuser that could result in overdose and death.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Withdrawal symptoms

Withdrawal symptoms may occur if tramadol/paracetamol tablets is discontinued. Reported symptoms have included anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhoea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been reported less frequently with tramadol/paracetamol tablets discontinuation include: panic attacks, severe anxiety, and paraesthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering tramadol/paracetamol tablets at the time of discontinuation.

Risk of seizures

Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with tramadol/paracetamol tablets only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper dose limit.

Use during anaesthesia

In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

Use in the elderly

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary, the dosage interval is to be extended according to the patient’s requirements.

Paediatric use

The effective and safe use of tramadol/paracetamol tablets has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Tramadol/paracetamol tablets should not be given to children aged less than 12 years or to those who weigh less than 37.5 kg. Dose reduction is required for patients with body weight less than 50 kg (see 4.2-Dose and method of administration)

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Concomitant use is contraindicated with:

- Non-selective MAO Inhibitors

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

- Selective-A MAO Inhibitors

Extrapolation from non-selective MAO inhibitors

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

- Selective-B MAO Inhibitors

Central excitation symptoms evocative of a serotoninergic 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.

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.

- Opioid agonists-antagonists (buprenorphine, 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:

- Serotonergic drugs: Concomitant use of tramadol and serotonergic drugs, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), MAO inhibitors, 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 >38ºC and inducible or ocular clonus. Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates: Increased risk of respiratory depression which can be fatal in cases of overdose.

- Other CNS depressants: Other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative

antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

• Warfarin: Periodic evaluation of prothrombin time should be performed when tramadol/paracetamol tablets and warfarin-like compounds are administered concurrently due to reports of increased INR.

• CYP450 interactions: Drugs that inhibit CYP2D6 isozyme may increase concentrations of tramadol and decrease concentrations of active metabolite M1.

Drugs that inhibit CYP3A4 isozyme may inhibit the metabolism of tramadol and probably M1. The clinical importance of these potential interactions has not been studies. The CYP-mediated metabolism of tramadol may be inhibited in vivo by amitryptyline, fluoxetine and norfluoxetine.

• Drugs reducing the seizure threshold: Tramadol can induce convulsions and increase the potential for serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol). The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

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

• Busulfan: Busulfan is eliminated from the body via conjugation with glutathione. Concomitant use with paracetamol may result in reduced busulfan clearance.

• Diflunisal: concomitant diflunisal increases paracetamol plasma concentrations and this may increase hepatotoxicity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility studies with the fixed combination (tramadol and paracetamol) have not been performed. No effect on fertility has been observed after oral administration of tramadol to male and female rats at respective doses up to 50 and 75 mg/kg/day. Mice continuously exposed to paracetamol 1430 mg/kg/day in the diet showed effects in offspring (fewer pups, retarded growth, increased abnormal sperm). The clinical significance of these findings is unknown.

Use in pregnancy (Pregnancy Category C)

Since tramadol/paracetamol tablets is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

• Data regarding paracetamol: Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages.

• Data regarding tramadol: Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol in pregnant women. Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Long-

term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

Oral administration of the tramadol/paracetamol combination to rats during the period of organogenesis elicited embryofetal toxicity at materno-toxic doses (at 50/434 mg/kg tramadol/paracetamol or 1.5 times the maximal recommended clinical dose on a mg/m2 basis), but no teratogenicity was observed. Oral administration of tramadol alone during organogenesis to rats (up to 75 mg/kg/day) and rabbits (up to 175 mg/kg/day) was associated with embryofetal toxicity (reduced fetal and placental weight, delayed ossification) along with maternal toxicity. Mice continuously exposed to paracetamol alone (1430 mg/kg/day in the diet) showed offspring effects (fewer pups, retarded growth, increased abnormal sperm) but no teratogenicity was observed in these studies.

Use in lactation

Since tramadol/paracetamol tablets is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

- Data regarding paracetamol: Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only paracetamol.

- Data regarding tramadol: Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol should not be ingested during breast feeding.

Animal studies with fixed combination (tramadol and paracetamol) have not been performed. Oral administration of tramadol to rats from late gestation to weaning at 80 mg/kg/day (2.5 times the maximal recommended clinical dose on a mg/m2 basis) was associated with clinical toxicity in pups, including reduced survival and weight gain; the no-effect dose was 40 mg/kg/day.

Tramadol is excreted into milk. The use of tramadol/paracetamol tablets during breastfeeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tramadol 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Table 1 shows the most frequent (>1%) treatment emergent adverse events (independent from causal relationship) observed in pooled clinical trials with tramadol/paracetamol tablets versus tramadol alone.

Table 1: Incidence of treatment emergent adverse events (>1%) with tramadol/paracetamol versus tramadol alone, stratified by age category

		All Subjects[a]		Elderly Subjects (≥65 years)	
Adverse Event		**Tram/Para (N=1437[b])**	**Tramadol Alone (N=694[c])**	**Tram/Para (N=503)**	**Tramadol Alone (N=455)**
Constipation		11%	41%	15%	49%
Nausea		18%	41%	17%	40%
Headache		11%	31%	9%	30%

Dizziness		15%	29%	15%	30%
Somnolence		12%	21%	12%	23%
Vomiting		6%	18%	7%	19%
Dyspepsia		5%	12%	5%	9%
Diarrhoea		6%	10%	9%	11%
Abdominal pain		3%	10%	4%	11%
Dry mouth		5%	9%	5%	7%
Anorexia		2%	8%	3%	9%
Flatulence		2%	4%	1%	4%
Tremor		1%	5%	1%	6%
Pain		2%	5%	2%	6%
Asthenia		1%	14%	2%	17%
Depression		2%	5%	2%	3%
Anxiety		2%	3%	1%	3%
Confusion		1%	4%	1%	4%
Nervousness		1%	5%	1%	5%

[a]All subjects exposed to tramadol/paracetamol during the double-blind and/or open-label phases.
[b]Includes subjects treated with tramadol/paracetamol combination in TRAMAP-ANAG-006, 008, 009, and 015. The average daily dose of tramadol delivered as tramadol/paracetamol in these trials ranged from 131 mg to 176 mg.
[c]Includes subjects treated with tramadol alone in TKM, TL2, and TKB.
The average daily dose of tramadol in these trials ranged from 227.5 mg to 258.5 mg.

The safety profile of tramadol/paracetamol tablets is characterised by the following adverse reactions. The most commonly adverse reactions were nausea, dizziness and somnolence, observed in more than 10% of the patients. All adverse reactions identified for tramadol/paracetamol tablets are listed below under the corresponding body organ systems according to the following classification: very common ≥ 10%; common ≥1% to <10%; uncommon ≥0.1% to <1%; rare ≥0.01% to <0.1%.

Cardiac disorders:

- Uncommon: arrhythmia, tachycardia, palpitations, syncope.

Vascular disorders:

- Uncommon: hypertension, hot flush.

Central and peripheral nervous system disorders:

- Very common: dizziness, somnolence
- Common: headache, trembling
- Uncommon: muscle contractions involuntary, paraesthesia, tinnitus
- Rare: ataxia, convulsions, speech disorders.

Psychiatric disorders:

- Common: confusional state, mood altered (anxiety, nervousness, euphoric mood) sleep disorders
- Uncommon: depression, hallucinations, nightmares, amnesia
- Rare: delirium, drug dependence.
- Post marketing surveillance: very rare: abuse.

Eye disorders:

- Rare: vision blurred, miosis, mydriasis

Respiratory, thoracic and mediastinal system disorders:

- Uncommon: dyspnoea

Gastrointestinal disorders:

- Very common: nausea
- Common: vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence
- Uncommon: dysphagia, melaena

Skin and subcutaneous tissue disorders:

- Common: hyperhidrosis, pruritus
- Uncommon: dermal reactions (e.g. rash, urticaria)

Urinary system disorders:

- Uncommon: albuminuria, micturition disorders (dysuria and urinary retention).

General disorders and administration site conditions:

- Uncommon: chills, chest pain.

Investigations:

- Uncommon: transaminases increased

Although not observed during clinical trials, the occurrence of the following adverse effects known to be related to the administration of tramadol or paracetamol 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.
- Rare cases (≥1/10000 to <1/1000) : allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
- Rare cases (≥1/10000 to <1/1000) : 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.
- Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Paracetamol

- Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

- 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.
- Patients with chronic or active hepatic disease, especially those with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration are more likely to experience hepatic toxicity from the paracetamol component of tramadol/paracetamol tablets. The maximum dose of tramadol/paracetamol tablets must not be exceeded in these patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Tramadol/paracetamol tablets contains a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

Symptoms of overdose from tramadol:

In principle, on intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular, miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Symptoms of overdose from paracetamol:

In paracetamol overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycaemic coma, and coagulation defects also may occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In the treatment of paracetamol overdose, gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum paracetamol levels should be obtained immediately if the patient presents 4 or more hours after ingestion to assess potential risk of hepatotoxicity; paracetamol levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose-dependent and occurs early in the course of intoxication.

Emergency treatment:

- Transfer immediately to a specialised unit.
- Maintain respiratory and circulatory functions.
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.

- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with tramadol/paracetamol tablets with haemodialysis or haemofiltration alone is not suitable for detoxification.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Tramadol, combinations

ATC code: N02A X 52

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non-selective agonist of the μ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an anti-tussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. The effect of tramadol on gastro-intestinal motility is lower than with pure opioid analgesics. At therapeutic doses, tramadol has no clinically significant effect on left ventricular function or cardiac index. Orthostatic changes in blood pressure have been observed. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

Antagonism studies demonstrated that both opioid and non-opioid properties of tramadol contribute to its analgesic activity.

Apart from analgesia, tramadol may produce other symptoms similar to that of opioids including: dizziness, somnolence, nausea, constipation, sweating and pruritus

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

Tramadol/paracetamol tablets are positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

Clinical trials

Acute Pain

A total of 1200 subjects (400 / study) aged over 16 years with moderate or severe pain following an oral surgical procedure (extraction of 2 ipsilateral, or >2, third molars requiring bone removal) were enrolled. Subjects were stratified by baseline pain severity: moderate or severe, and received one of 5 single-dose treatments (tramadol / paracetamol 75 mg / 650

mg, tramadol 75 mg, paracetamol 650 mg, ibuprofen 400 mg or placebo). Subjects could receive a supplemental analgesic during the studies. If a subject took rescue medication or discontinued prematurely, remaining observations points were filled using the last observation carried forward (LOCF) method.

Across the studies most subjects were female (55-63%) and Caucasian (75-93%). Mean age was 21.1 – 21.7 years (range 16-46 years). Baseline pain intensity was consistent across the studies (moderate for 66-70%, severe for 30-34%); mean rating (6.1-6.2); and the majority of subjects had 4 molars removed (64-83%). 64% to 74% of subjects given T/A 75/650 in the pivotal studies required additional analgesia at least once during the study. Table 2 presents the primary summary efficacy variables (TOTPAR, SPID, and SPRID) and statistical comparisons for the intervals, 0-4 hours, and 0-8 hours, for each of these studies.

Table 2: Primary summary efficacy variables: TOTPAR, SPID and SPRID scores, pivotal studies: T-A-010, T-A-012, T-A-013, efficacy analysis groups

Variable	Treatment	N	0 – 4h			0 – 8 h		
			Mean (SD)	T/A vs component	Active vs PBO	Mean (SD)	T/A vs component	Active vs PBO
Study T-A-010								
TOTPAR	T/A	80	7.7(4.12)		<0.001	13.7(8.19)		<0.001
	T75	78	4.3(4.26)	<0.001	0.001	8.1(8.45)	<0.001	<0.001
	APAP650	80	6.5(4.11)	0.032	<0.001	10.1(7.13)	0.002	<0.001
	IBU400	80	7.6(4.69)		<0.001	13.6(9.09)		<0.001
	PBO	79	2.2(3.02)			3.7(6.02)		
SPID	T/A	80	3.1(2.94)		<0.001	5.0(5.95)		<0.001
	T75	78	1.1(3.17)	<0.001	0.001	1.8(6.48)	<0.001	0.001
	APAP650	80	2.4(2.81)	0.066	<0.001	3.1(5.00)	0.017	<0.001
	IBU400	80	3.3(3.39)		<0.001	5.6(6.42)		<0.001
	PBO	79	-0.3(2.20)			-1.1(4.53)		
SPRID	T/A	80	10.8(6.75)		<0.001	18.7(13.47		<0.001
	T75	78	5.3(7.10)	<0.001	0.001	10.0(14.22	<0.001	<0.001
	APAP650	80	8.9(6.67)	0.037	<0.001	13.1(11.53	0.003	<0.001
	IBU400	80	10.9(7.80)		<0.001	19.2(14.89		<0.001
	PBO	79	1.8(4.86)			2.6(9.73)		
Study T-A-012								
TOTPAR	T/A	8	6.8(4.92)		<0.001	11.1(9.72)		<0.001
	T75	8	2.7(3.85)	<0.001	0.031	5.0(8.31)	<0.001	0.024
	APAP650	8	5.4(4.11)	0.019	<0.001	7.5(7.35)	0.003	<0.001
	IBU400	8	6.9(4.89)		<0.001	12.7(9.80)		<0.001
	PBO	8	1.5(2.70)			2.4(5.43)		
SPID	T/A	8	2.9(3.19)		<0.001	4.7(6.46)		<0.001
	T75	8	0.4(2.66)	<0.001	0.028	0.4(5.82)	<0.001	0.018
	APAP650	8	2.3(2.66)	0.096	<0.001	2.9(4.75)	0.026	<0.001
	IBU400	8	2.9(3.61)		<0.001	5.2(6.91)		<0.001
	PBO	8	-0.5(2.42)			-1.5(4.91)		
SPRID	T/A	8	9.6(7.86)		<0.001	15.8(15.7		<0.001
	T75	8	3.1(6.23)	<0.001	0.025	5.4(13.52)	<0.001	0.017
	APAP650	8	7.7(6.51)	0.033	<0.001	10.4(11.6	0.006	<0.001
	IBU400	8	9.8(8.23)		<0.001	17.9(16.1		<0.001
	PBO	8	0.9(4.75)			0.8(9.50)		
Study T-A-013								
TOTPAR	T/A	8	7.0(5.01)		<0.001	11.4(10.4		<0.001
	T75	8	3.3(4.40)	<0.001	0.066	7.0(10.03)	0.002	0.020
	APAP650	8	5.6(5.12)	0.033	<0.001	8.2(9.53)	0.020	0.002
	IBU400	8	8.2(5.15)		<0.001	14.6(10.8		<0.001
	PBO	8	2.2(3.96)			3.8(7.85)		

SPID	T/A	8	2.9(3.61)		<0.001	4.4(7.50)		<0.001
	T75	8	0.2(3.52)	<0.001	0.034	0.6(7.64)	<0.001	0.012
	APAP650	8	2.0(3.71)	0.046	<0.001	2.2(7.07)	0.032	<0.001
	IBU400	8	3.8(3.67)		<0.001	6.7(7.82)		<0.001
	PBO	8	-0.8(3.15)			-2.1(6.70)		
SPRID	T/A	8	9.9(8.38)		<0.001	15.8(17.4		<0.001
	T75	8	3.5(7.65)	<0.001	0.045	7.5(17.14)	<0.001	0.013
	APAP650	8	7.6(8.58)	0.034	<0.001	10.4(15.9	0.021	<0.001
	IBU400	8	12.0(8.58)		<0.001	21.3(18.2		<0.001
	PBO	8	1.3(6.82)			1.7(13.94)		

Chronic Pain

Efficacy of tramadol/paracetamol tablets in the relief of chronic pain has not been examined in comparison to tramadol and/or paracetamol given alone. Efficacy and safety of tramadol/paracetamol tablets in patients with chronic pain was examined in 5 placebo-controlled, multiple-dose studies conducted over 3 months (CAPSS-104, CAPSS-112, CAPSS-113, CAPSS-114 and PRI/TRP/CAN1). Subjects were primarily 40-75 years of age and taking a stable daily dose of an NSAID for at least 3 months before study entry. In CAPSS-114, subjects who had been taking a COX-2 selective inhibitor for pain relief were permitted to continue taking it while in the trial. Mean pain severity ranged from 67.8 mm to 80.1 mm, on a standard pain visual analogue (PVA) scale, 0-10 mm. Study drug was titrated from one (tramadol HCl 37.5 mg with paracetamol 325 mg) to 4 tablets / day over the first 10 days, followed by a regimen of 1 or 2 tablets every 4 to 6 hours, as needed. The maximum dose allowed was 8 tablets / day (tramadol HCl 300 mg with paracetamol 2600 mg).

Tramadol/paracetamol tablets was statistically superior to placebo in lowering the PVA score in PRI/TRP/CAN1 and CAPSS-112 and CAPSS-114, and in increasing the time to discontinuation due to efficacy failure in CAPSS-113 and PRI/TRP/CAN1. Statistical significance in lowering the PVA score was not demonstrated in CAPSS-114.

The efficacy of tramadol/paracetamol tablets in the treatment of patients with cancer has not been investigated in clinical trials.

5.2 PHARMACOKINETIC PROPERTIES

Tramadol is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

After a single oral administration of a tramadol/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/mL [(+)-tramadol/(-)-tramadol] and 4.2 µg/mL (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives t1/2 are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2.5 h (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of tramadol/paracetamol tablets, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75%. After repeated administration, the bioavailability is increased and reaches approximately 90%.

After administration of tramadol/paracetamol tablets, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration of tramadol/paracetamol tablets with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that tramadol/paracetamol tablets can be taken independently of meal times.

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 relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism

Tramadol is extensively metabolised after oral administration. About 30% of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Tramadol is metabolised through O-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing.

Paracetamol is principally metabolised in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P 450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Excretion

Tramadol and its metabolites are eliminated mainly by the kidneys. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulfo-conjugate derivatives. Less than 9% of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

Use in the elderly

Population PK and dedicated PK studies using tramadol alone did not reveal a relevant effect of age on the PK of tramadol up to the age of 75 years. Above the age of 75 years the elimination half-life of tramadol was slightly prolonged by about 15% and exposure (AUC) increased by about 50% in comparison to subjects aged between 65 – 75 years.

Use in children

The pharmacokinetics of tramadol/paracetamol tablets has not been studied in children or adolescents aged under I6 years.

Use in renal impairment

The pharmacokinetics of tramadol/paracetamol tablets has not been studied in patients with renal impairment. Based on studies using tramadol alone, excretion of tramadol and its metabolite M1 is reduced in patients with CKD stages 4 or 5.

Use in hepatic impairment

The pharmacokinetics of tramadol/paracetamol tablets has not been studied in patients with hepatic impairment. Tramadol and paracetamol are both extensively metabolised by the liver. In patients with severe hepatic impairment tramadol/paracetamol should not be used.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies with the fixed combination (tramadol and paracetamol) have not been performed. There was no evidence of genotoxicity with tramadol in a standard battery of in vitro and in vivo tests. Paracetamol can cause chromosomal damage in vitro and in vivo, but only at high concentrations or at large doses associated with hepatotoxicity.

Carcinogenicity

Carcinogenicity studies with the fixed combination (tramadol and paracetamol) have not been performed.

Results of carcinogenicity tests do not suggest a potential risk of tramadol for man.

Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 INCOMPATIBILITIES

See Section 4.5-Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

APO-Tramadol/Paracetamol 37.5/325 is packaged in PVC/PVDC-Al blister pack, in pack sizes of 20 or 50 film-coated tablets (AUST R 280699).

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

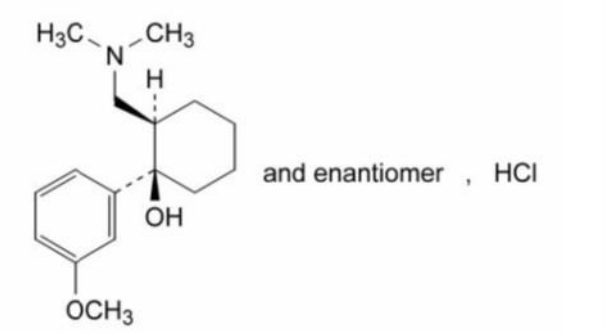
Tramadol hydrochloride is an odourless, white to off-white crystalline powder that is freely soluble in water and in methanol, very slightly soluble in acetone and has a pKa of 9.41. The water/n-octanol partition coefficient (logP) is 1.35 at pH 7.

Paracetamol is a white or almost white, crystalline powder; sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride (15-25°C) and has a pKa of 9.5 at 25°C. The partition coefficient (logP) is 0.51.

Chemical structure

Tramadol hydrochloride

Structural Formula:



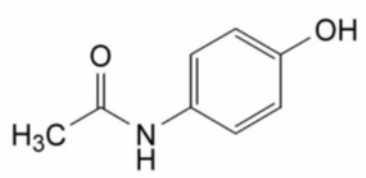
Chemical Name: (1RS,2RS)-2-[(dimethylamino)methyl]-1-(3 methoxyphenyl)cyclohexanol hydrochloride

Molecular Formula: $C_{16}H_{25}NO_2$.HCl

Molecular Weight: 299.84

Paracetamol

Structural Formula:



Chemical Name: N-(4-Hydroxyphenyl)acetamide

Molecular Formula: $C_8H_9NO_2$

Molecular Weight: 151.2

CAS number

Tramadol hydrochloride : 36282-47-0

Paracetamol : 103-90-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

22 February 2018

10 DATE OF REVISION

22 October 2018

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information
2,3	Minor editorial changes Update of the tablet appearance to align with the updated specifications.