1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA
(Paracetamol 325 mg and Tramadol 37,5 mg) Tablets

PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA
(Paracetamol 650 mg and Tramadol 75 mg) Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA:

Each tablet contains 325 mg paracetamol and 37,5 mg tramadol hydrochloride.

Sugar free

PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA:

Each tablet contains 650 mg paracetamol and 75 mg tramadol hydrochloride.

Sugar free

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA:

White, oblong, scored tablets having a length and width of 15 mm and 6,5 mm respectively.

PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA:

White, oblong, scored tablets having a length and width of 18 mm and 8,5 mm respectively.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARACETAMOL/TRAMADOL CIPLA is indicated for the management of moderate to moderately severe pain in adults.

PARACETAMOL/TRAMADOL CIPLA is not recommended for minor pain that may be treated adequately through lesser means.

4.2 Posology and method of administration

Posology

PARACETAMOL/TRAMADOL CIPLA is to be used in adults and children over 16 years of age.

THE RECOMMENDED DOSE SHOULD NOT BE EXCEEDED.

A titration period of several days with gradual dose increases at the commencement of PARACETAMOL/TRAMADOL CIPLA therapy can be useful for some patients. The tolerability of tramadol in patients with moderate to moderately severe chronic pain can be improved by initiating treatment on tramadol at a low dose and slowly increasing the dose to achieve sufficient pain relief.

Adults and adolescents (16 years and older)

For the management of pain, the recommended dose of:

- PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA is 1 or 2 tablets every 4 to 6 hours, as needed for pain relief, up to a maximum of 8 tablets per day.
- PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA is ½ or 1 tablet every 4 to 6 hours, as needed for pain relief, up to a maximum of 4 tablets per day.

Tramadol/paracetamol should under no circumstances be administered for longer than is strictly necessary (see also section 4.4).

Paediatric population

PARACETAMOL/TRAMADOL CIPLA can be used in children who are 16 years of age and older. The safe and effective use has not been established in children below this age.

Renal insufficiency / dialysis

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

For patients with creatinine clearance < 30 mL/min, the dosing interval of:

- PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA should be increased not to exceed 2 tablets every 12 hours.
- PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA should be increased not to exceed 1 tablet every 12 hours.

Hepatic impairment

PARACETAMOL/TRAMADOL CIPLA should not be used in patients with severe liver impairment. (See Section 4.3)

Method of administration

Oral use

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

4.3 Contraindications

- Known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Acute intoxication with alcohol, hypnotic drugs, centrally acting analgesics, opioids or psychotropic drugs.
- PARACETAMOL/TRAMADOL CIPLA should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5.).
- Severe hepatic impairment.
- Epilepsy not controlled by treatment (see section 4.4. Special Warnings).
- Narcotic withdrawal treatment (see section 4.4 Special Warnings).

- Patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
- Patients with increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.

4.4 Special warnings and precautions for use

Warnings:

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.

- In adults and adolescents 16 years and older. The maximum dose of 8 tablets of PARACETAMOL/TRAMADOL CIPLA 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 the counter) or tramadol hydrochloride containing products concurrently without the advice of a doctor.
- In severe renal insufficiency (creatinine clearance <10 mL/mm), PARACETAMOL/TRAMADOL CIPLA is not recommended.
- In patients with severe hepatic impairment PARACETAMOL/TRAMADOL CIPLA should not be used (See section 4.3). The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases prolongation of dosage interval should be carefully considered.
- In severe respiratory insufficiency, tramadol/paracetamol is not recommended.
- Tramadol in PARACETAMOL/TRAMADOL CIPLA is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.
- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5).
- PARACETAMOL/TRAMADOL CIPLA should not be taken with alcohol containing beverages.
- Paracetamol in overdosage may cause hepatic toxicity.

- Tramadol /paracetamol should be used with caution in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an 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 reuptake inhibitors, MAO-inhibitors, antipsychotics, centrally acting analgesics, or local anaesthetics. The risk of seizures may also be increased in patients with epilepsy, with a history of seizures or in patients with a 5ecognized 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:

Tolerance and physical and/or psychological dependence may develop, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly (see section 4.2).

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 opioid-dependent patients and patients with a tendency to drug abuse, and a history of drug abuse or dependence, treatment with PARACETAMOL/TRAMADOL CIPLA is not recommended.

Withdrawal:

Withdrawal symptoms may occur if PARACETAMOL/TRAMADOL CIPLA is discontinued abruptly.

Symptoms of withdrawal reaction, similar to those occurring during opiate withdrawal, may occur even at therapeutic doses and for short term treatment (see section 4.8). Panic attacks, severe anxiety, hallucinations, paraethesia, tinnitus, and unusual CNS symptoms have also been reported with abrupt discontinuation of tramadol hydrochloride. Withdrawal symptoms may be avoided by tapering it at the time of discontinuation especially after long treatment periods.

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 PARACETAMOL/TRAMADOL CIPLA should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Use with CNS depressants:

The administration of PARACETAMOL/TRAMADOL CIPLA 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.

Hyponatraemia:

Hyponatraemia has been reported with the use of PARACETAMOL/TRAMADOL CIPLA, 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 PARACETAMOL/TRAMADOL CIPLA and appropriate treatment (e.g., fluid restriction). During PARACETAMOL/TRAMADOL CIPLA treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Use with general anaesthetics:

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.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use is contraindicated with:

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.

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, 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 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 and serotonergic drugs 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.

• Other central nervous system depressants, such as 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. These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

• As medically appropriate, periodic evaluation of prothrombin time should be performed when tramadol /paracetamol and warfarin like compounds are administered concurrently due to reports of increased INR.

• 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

PARACETAMOL/TRAMADOL CIPLA should not be used during pregnancy.

• **Data regarding paracetamol:**

Epidemiological studies in human pregnancy have shown no teratogenic 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.

Breast-feeding

PARACETAMOL/TRAMADOL CIPLA should not be used 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:**

Approximately 0,1 % of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3 % of the maternal weight-adjusted dosage. For this reason, tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility.

Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol.

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. This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently reported undesirable effects of paracetamol/tramadol combination in clinical trials were gastrointestinal and central nervous system effects. Nausea, dizziness, and somnolence were observed in more than 10 % of patients.

b) Tabulated summary of adverse reactions

The following adverse reactions are reported corresponding to: *Frequent, Less frequent and Frequency unknown.* Furthermore, the adverse reactions are presented as the combination tablet PARACETAMOL/TRAMADOL CIPLA (Paracetamol and Tramadol) and thereafter by the individual active ingredients.

Table 1 Paracetamol and Tramadol (PARACETAMOL/TRAMADOL CIPLA) combination tablet

Frequent	***Less frequent***	***Frequency Unknown***
Metabolism and nutrition disorders		
		Hypoglycaemia
Psychiatric disorders		
Confusional state, mood altered, anxiety, nervousness, euphoria mood, sleep disorders	Depression, hallucinations, nightmares, delirium, drug dependence	
Nervous system disorders		
Dizziness, somnolence, headache trembling	Involuntary muscular contractions, paraesthesia, amnesia, ataxia, convulsions, syncope, speech disorders	
Eye disorders		
	Vision blurred, miosis, mydriasis	
Ear and labyrinth disorders		
	Tinnitus	
Cardiac disorders		
	Palpitations, tachycardia, arrythmia	
Vascular disorders		
	Hypertension, hot flush	
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	
Gastro-intestinal disorders		
Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence	Dysphagia, melaena	
Skin and subcutaneous tissue disorders		

Table 1 Paracetamol and Tramadol (PARACETAMOL/TRAMADOL CIPLA) combination tablet

Frequent	***Less frequent***	***Frequency Unknown***
Hyperhidrosis, pruritus	Dermal reactions (e.g.rash, urticaria).	
Renal and urinary disorders		
	Albuminuria, micturition disorders (dysuria and urinary retention)	
General disorders and administration site conditions		
	Chills, chest pain	
Investigations		
	Transaminases Increased	

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or paracetamol cannot be excluded.

Tramadol

- Postural hypotension, bradycardia, collapse.
- Post-marketing surveillance of tramadol has revealed elevated creatinine and rare alterations of warfarin effect, including elevation of prothrombin times.
- Hepatitis

  Less frequent: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema), Steven Johnson syndrome and anaphylaxis
- *Less frequent*: changes in appetite, motor weakness, and respiratory depression
- Psychic adverse 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), suicidal tendencies 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 hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.
- Very rare 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. In addition, suspected adverse reactions may also be reported by e-mail to drugsafetysa@cipla.com or by telephone to 080 222 6662 (toll free).

4.9 Overdose

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

Symptoms of overdose from tramadol:

The initial symptoms of tramadol overdosage may include respiratory depression up to respiratory arrest and/or seizures. These include in particular, miosis, vomiting, cardiovascular collapse and coma. Symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. 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 I barbiturates). Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with tramadol/paracetamol with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

Symptoms of overdose from paracetamol:

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and 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.

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.

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:

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.

Naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.

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.

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).

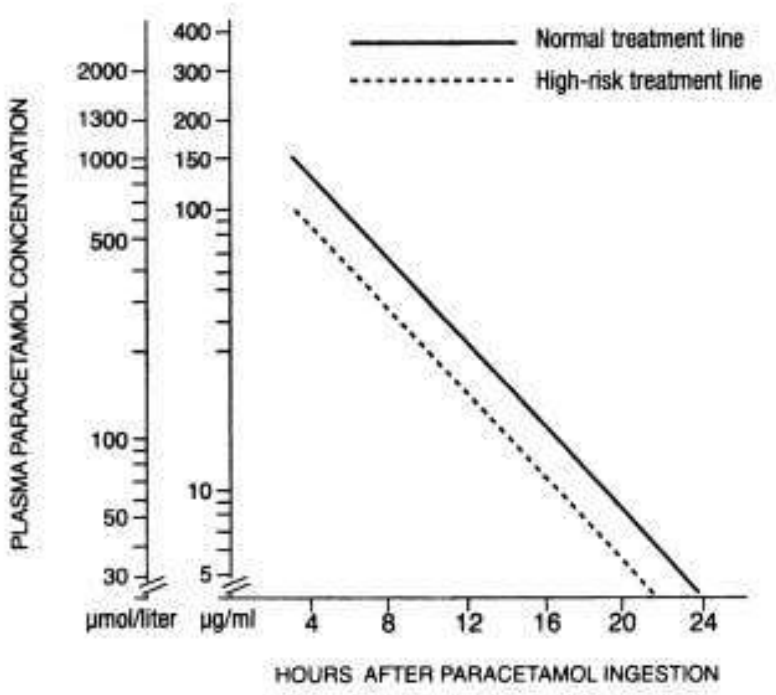
In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

A.2.9. Other analgesics

ATC code: N02A J 13 ANALGESICS

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.

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

5.2 Pharmacokinetic properties

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration, reaching peak activity in 2 to 3 hours. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %. Oral absorption of paracetamol gives a peak plasma concentration within one hour and is not affected by co-administration with tramadol.

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

Distribution

Tramadol has a high tissue affinity (Vd,β=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 %) of paracetamol is bound to plasma proteins.

Metabolism

Tramadol and paracetamol are both extensively metabolised in the liver. 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 metabolised 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.

Elimination

About 30 % of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Tramadol and its metabolites are eliminated mainly by the kidneys. The plasma elimination half-lives of tramadol and its M1 metabolite are approximately 6 and 7 hours respectively.

Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. 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. Less than 9 % of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

pregelatinised maize starch

sodium potato starch glycolate (Type A)

magnesium stearate

colloidal anhydrous silica

povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years in aluminium/polyethylene strips and PVC/PVDC blister strips.

6.4 Special precautions for storage

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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA:

Carton containing 60 tablets packed either in 15 aluminium/polyethylene strips of 4 tablets each or 6 PVC/PVDC blister strips of 10 tablets each.

PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA:

Carton containing 30 tablets packed either in 3 aluminium/polyethylene strips or PVC/PVDC blister strips of 10 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Parc du Cap

Building 9, Mispel Street

Bellville, RSA, 7530

8. REGISTRATION NUMBER(S)

PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA: 48/2.9/0066

PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA: 48/2.9/0067

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 March 2022

10. DATE OF REVISION OF THE TEXT

Not applicable.