PROFESSIONAL INFORMATION FOR

PARACETAMOL/TRAMADOL CIPLA

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

PARACETAMOL/TRAMADOL 325 mg/37,5 mg CIPLA

Paracetamol 325 mg and tramadol hydrochloride 37,5 mg tablets

PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA

Paracetamol 650 mg and tramadol hydrochloride 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.

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.

PARACETAMOL/TRAMADOL 650 mg/75 mg CIPLA:

White, oblong, scored tablets that can be split into two halves of 325/37,5 mg each.

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 may be beneficial 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.

The lowest effective dose should be used for the shortest period of time. Tramadol/paracetamol should under no circumstances be administered for longer than is strictly necessary (see also **section 4.4**).

Special populations

Elderly (65 years of age and older)

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

Renal impairment

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

The use of PARACETAMOL/TRAMADOL CIPLA in patients with moderate to severe hepatic impairment is contraindicated.

Paediatric population

Children below 16 years of age

The use of PARACETAMOL/TRAMADOL CIPLA is contraindicated in children below 12 years of age (see **section 4.3**). The safety and effectiveness of PARACETAMOL/TRAMADOL CIPLA in children aged 12 to below 16 years of age has not been established (see **section 4.3, 4.4**).

Method of administration

Oral use.

Tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed. PARACETAMOL/TRAMADOL CIPLA can be administered without regard to food.

4.3 Contraindications

PARACETAMOL/TRAMADOL CIPLA is contraindicated in:

- patients with known hypersensitivity to paracetamol, tramadol, other opioids such as codeine or to any of the excipients in PARACETAMOL/TRAMADOL CIPLA (see **section 6.1**).
- acute intoxication with alcohol, hypnotic drugs, centrally acting analgesics, opioids or psychotropic drugs.
- moderate to severe hepatic impairment.
- patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal (see **section 4.5**).
- narcotic withdrawal treatment (see **section 4.4**).
- patients with respiratory depression.

- patients with head injury or cerebral disease, with or without increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.
- patients with epilepsy or seizures of any cause as PARACETAMOL/TRAMADOL CIPLA can cause seizures (convulsions) (see **section 4.4**).
- children younger than 12 years of age.
- children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

4.4 Special warnings and precautions for use

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 only take paracetamol containing products under medical supervision.

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.

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 in overdosage may cause hepatic toxicity.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

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 centre or the respiratory function, or with an increased intracranial pressure.

Seizures

PARACETAMOL/TRAMADOL CIPLA should not be used in patients with a history of epilepsy or those susceptible to seizures (see **section 4.3**). 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 concomitantly taking tricyclic anti-depressants or other tricyclic compounds e.g. selective serotonin reuptake inhibitors (SSRI, antidepressants or anorectics), MAO-inhibitors, opioids, other medicines that reduce the seizure threshold and neuroleptics.

The risk of seizures may also be increased in patients with epilepsy, with a history of seizures or in patients with a recognized risk for seizures e.g. drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramadol overdose.

Anaphylactic reactions

Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and therefore should not receive PARACETAMOL/TRAMADOL CIPLA.

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

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

Respiratory depression

Opioids (as contained in PARACETAMOL/TRAMADOL CIPLA) can cause sleep-related breathing disorders such as sleep apnoea syndromes (including central sleep apnoea [CSA]) and hypoxia (including sleep-related hypoxia) (see **section 4.8**). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep

apnoea or a worsening of an existing sleep apnoea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see **section 4.4**). In severe respiratory insufficiency, tramadol/paracetamol is not recommended.

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 (see **section 4.9**). Alternative medication, dose reduction and/or increased monitoring for signs of tramadol toxicity, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Even at labeled dosage regimens, individuals who are ultra-rapid metabolisers may have life-threatening or fatal respiratory depression or experience signs of toxicity such as extreme sleepiness, confusion, or shallow breathing (see **section 4.9**).

Other risk factors for life-threatening respiratory depression in children

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Based upon post marketing reports with tramadol, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol (see **section 4.3**). Furthermore, children with obstructive sleep

apnoea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect (see **section 4.3**). Because of the risk of life-threatening respiratory depression and death, avoid the use of PARACETAMOL/TRAMADOL CIPLA in adolescents younger than 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnoea and concomitant use of other medicines that cause respiratory depression. Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

As with adults, when prescribing opioids for adolescents, health care providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and signs of opioid overdose (see **section 4.2**).

Adrenal insufficiency

Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Use with Central Nervous System (CNS) depressants, including alcohol

The concomitant use of tramadol with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression. PARACETAMOL/TRAMADOL CIPLA should not be taken with alcohol containing beverages. PARACETAMOL/TRAMADOL CIPLA should be used with caution and in reduced dosages when administered to patients receiving CNS depressants (see **section 4.5**).

Drug dependence and potential for abuse

PARACETAMOL/TRAMADOL CIPLA has a dependence potential and tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop with its use.

The medicine has been associated with craving, drug-seeking behaviour and tolerance development. Cases of abuse and dependence on tramadol have been reported. PARACETAMOL/TRAMADOL CIPLA should not be used in opioid-dependent patients. PARACETAMOL/TRAMADOL CIPLA 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 PARACETAMOL/TRAMADOL CIPLA is not recommended. PARACETAMOL/TRAMADOL CIPLA should not be given to patients who are suicidal or prone to addiction.

CAUTION SHOULD BE PRACTICED IN PATIENTS WITH A PERSONAL AND FAMILY HISTORY OF MENTAL HEALTH DISORDERS OR SUBSTANCE ABUSE AS THEY ARE AT AN INCREASED RISK FOR ADDICTION AND ABUSE.

Increased risk of hepatotoxicity with alcohol use

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

Withdrawal

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

Panic attacks, severe anxiety, hallucinations, paraesthesia, 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.

Use with serotonergic medicines

Use PARACETAMOL/TRAMADOL CIPLA with great caution in patients taking serotonergic medicines including SSRIs. Concomitant use of tramadol with serotonergic medicines including SSRIs increases the risk of adverse events, including seizure and serotonin syndrome (see **section 4.5**).

Renal Impairment

PARACETAMOL/TRAMADOL CIPLA has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing

interval of PARACETAMOL/TRAMADOL CIPLA be increased not to exceed 2 tablets every 12 hours.

In severe renal insufficiency (creatinine clearance <10 mL/min), PARACETAMOL/TRAMADOL CIPLA is not recommended.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing medicines. If a patient develops SCAR, treatment with PARACETAMOL/TRAMADOL CIPLA must immediately be discontinued and appropriate treatment instituted.

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.

Precautions – general

The recommended dose of PARACETAMOL/TRAMADOL CIPLA should not be exceeded.

Do not co-administer PARACETAMOL/TRAMADOL CIPLA with other tramadol or paracetamol containing products.

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

Inhibitors of CYP2D6	
Mechanism	Enzyme inhibition in decreased rate of metabolism of tramadol
Clinical impact	The concomitant use of PARACETAMOL/TRAMADOL CIPLA and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of PARACETAMOL/TRAMADOL CIPLA is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to

	tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping an inhibitor of CYP2D6, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity and may cause potentially fatal respiratory depression.
Intervention	If concomitant use of an inhibitor of CYP2D6 is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome (see **section 4.4**) If an inhibitor of CYP2D6 is discontinued, consider lowering PARACETAMOL/TRAMADOL CIPLA dosage until stable medicine effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
Examples	Quinidine, fluoxetine, paroxetine, amitriptyline and bupropion
Inhibitors of CYP3A4	
Mechanism	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
Clinical impact	The concomitant use of PARACETAMOL/TRAMADOL CIPLA and an inhibitor of CYP3A4 can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. After

	stopping an inhibitor of CYP3A4, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease, resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.
Intervention	If concomitant use is necessary, consider dosage reduction of PARACETAMOL/TRAMADOL CIPLA until stable medicine effects are achieved. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of PARACETAMOL/TRAMADOL CIPLA is achieved. If an inhibitor of CYP3A4 is discontinued, consider increasing the PARACETAMOL/TRAMADOL CIPLA dosage until stable medicine effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
Examples	Macrolide antibiotics (e.g. erythromycin), azole-antifungal medicines (e.g. ketoconazole), protease inhibitors (e.g. ritonavir)
CYP3A4 Inducers	
Mechanism	Enzyme induction resulting in increased rate of metabolism of tramadol
Clinical impact	The concomitant use of PARACETAMOL/TRAMADOL CIPLA and an inducer of CYP3A4 can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping an inducer of CYP3A4, as the effects of the inducer decline, the

	tramadol plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.
Intervention	If concomitant use is necessary, consider increasing the PARACETAMOL/TRAMADOL CIPLA dosage until stable medicine effects are achieved. Follow patients for signs of opioid withdrawal. If an inducer of CYP3A4 is discontinued, consider PARACETAMOL/TRAMADOL CIPLA dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, an inducer of CYP3A4, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of PARACETAMOL/TRAMADOL CIPLA and carbamazepine is not recommended.
Examples	Rifampin, carbamazepine, phenytoin
Benzodiazepines and other central nervous system (CNS) depressants including alcohol	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical impact	The concomitant use of tramadol with central nervous system depressants, such as benzodiazepines and other sedatives/hypnotics, anaesthetic medicines, phenothiazines, tranquilisers, opioids or alcohol, may produce additive CNS depressant effects, such as profound sedation and respiratory depression. If concomitant use of PARACETAMOL/TRAMADOL CIPLA with a CNS

	depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both medicines, and follow patients closely for sign of respiratory depression. Due to additive pharmacodynamic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma and death.
Intervention	Reserve concomitant prescribing of these medicines for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **section 4.4**).
Examples	Benzodiazepines and other sedatives/hypnotics, tranquilisers, muscle relaxants, general anaesthetics, other opioids, alcohol
Serotonergic Medicines	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical impact	Concomitant use of tramadol with serotonergic medicines increases the risk of adverse events, including seizures and serotonin syndrome.
Intervention	Use caution when administering PARACETAMOL/TRAMADOL CIPLA in patients taking serotonergic medicines and monitor for signs of adverse events. Discontinue PARACETAMOL/TRAMADOL CIPLA if serotonin syndrome is suspected.
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine

	reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonist, medicines that affect the serotonin neurotransmitter system (e.g. mirtazapine and trazodone) and some muscle relaxants (e.g. cyclobenzaprine, metaxalone).
Monoamine Oxidase Inhibitors (MAOIs)	
Mechanism	Additive or synergistic pharmacodynamic effects
Clinical impact	The concomitant use of PARACETAMOL/TRAMADOL CIPLA with MAOIs, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see **section 4.3**). MAOI interactions with opioids may manifest as serotonin syndrome (see **section 4.4**) or opioid toxicity (e.g. respiratory depression, coma) (see **section 4.4**).
Intervention	Do not use PARACETAMOL/TRAMADOL CIPLA in patients taking MAOIs or within 14 days of stopping such treatment.
Examples	Phenelzine, tranylcypromine, linezolid
Warfarin	
Clinical impact	As medically appropriate, periodic evaluation of prothrombin time should be performed when PARACETAMOL/TRAMADOL CIPLA and these medicines are administered concurrently due to reports of increased International Normalized Ratio (INR) in some patients. Post-marketing surveillance of tramadol has revealed rare reports of alteration of

	warfarin effect, including elevation of prothrombin times. Paracetamol may produce hypoprothrombinaemia when administered with warfarin-like medicines.
Intervention	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.
Cimetidine	
Clinical impact	Concomitant administration of tramadol with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.
Opioid agonists-antagonists	
Clinical impact	Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.
Examples	buprenorphine, nalbuphine, pentazocine
5-HT3 antagonist: Ondansetron	
Clinical impact	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.
Flucloxacillin	
Clinical impact	Caution should be taken when paracetamol is used concomitantly with flucloxacillin, as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors (see **section 4.4**).

4.6 Fertility, pregnancy and lactation

Pregnancy

PARACETAMOL/TRAMADOL CIPLA should not be used during pregnancy.

Safe use in pregnancy has not been established.

PARACETAMOL/TRAMADOL CIPLA is not recommended for pregnant mothers because tramadol has been shown to cross the placenta and appears in breast milk.

The use of opioids during childbirth might result in respiratory depression in the newborn infant.

Prolonged use of PARACETAMOL/TRAMADOL CIPLA, or other opioids, during pregnancy may lead to neonatal opioid withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.

Breastfeeding

PARACETAMOL/TRAMADOL CIPLA should not be used during breastfeeding.

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 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*
Blood and lymphatic system disorder		
	Anaemia	
Metabolism and nutrition disorders		
	Weight decrease	Hypoglycaemia

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

Frequent	*Less frequent*	*Frequency Unknown*
Psychiatric disorders		
Confusional state, mood altered, anxiety, nervousness, euphoria mood, sleep disorders, anorexia, insomnia	Depression, hallucinations, nightmares, delirium, drug dependence, depersonalisation, emotional lability, impotence, abnormal thinking	
Nervous system disorders		
Dizziness, somnolence, headache, tremor	Involuntary muscular contractions, paraesthesia, amnesia, ataxia, convulsions, syncope, speech disorders, hypertonia, migraine, aggravated migraine, vertigo, stupor	
Eye disorders		
	Vision blurred, miosis, mydriasis, abnormal vision	
Ear and labyrinth disorders		
	Tinnitus	
Cardiac disorders		

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

Frequent	*Less frequent*	*Frequency Unknown*
	Palpitations, tachycardia, arrythmia, dysrhythmia	
Vascular disorders		
	Hypertension, aggravated hypertension, hypotension	
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	
Gastro-intestinal disorders		
Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence	Dysphagia, melaena, tongue oedema	
Hepato-biliary disorders		
	Liver test abnormalities, hepatitis	
Skin and subcutaneous tissue disorders		
Hyperhidrosis, pruritus, rash		Toxic epidermal necrolysis (TEN), Stevens-Johnson

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

Frequent	*Less frequent*	*Frequency Unknown*
		syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS)
Renal and urinary disorders		
	Albuminuria, micturition disorders (dysuria and urinary retention), oliguria	
General disorders and administration site conditions		
Asthenia, fatigue, hot flushes	Chills, chest pain, rigors, withdrawal syndrome	
Investigations		
	Transaminases Increased	

Agranulocytosis, leucopenia, neutropenia, pancytopenia, thrombocytopenia are rare and usually mild side effects experienced with paracetamol.

Table 2: Adverse reactions identified during post marketing experience with PARACETAMOL/TRAMADOL CIPLA

System organ class	Adverse reaction
Metabolism and nutrition disorders	Hyponatraemia/syndrome of inappropriate antidiuretic hormone
Immune system disorders	Fixed eruption

Tramadol

- postural hypotension, bradycardia, collapse, vasodilation, myocardial ischaemia, pulmonary oedema
- post-marketing surveillance of tramadol has revealed elevated creatinine and rare alterations of warfarin effect, including elevation of prothrombin times
- hepatitis, liver failure
- gastrointestinal bleeding

  Less frequent: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema), Stevens-Johnson Syndrome/TENS anaphylaxis and urticaria.
- *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), difficulty concentrating,

depression, 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.

• serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic medicines such as SSRIs and MAO inhibitors. Post marketing experience with the use of tramadol containing medicines included reports of delirium, miosis, mydriasis, and speech disorder and reports of movement disorder. Cases of hypoglycaemia 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 medicines that may cause hyponatraemia.

• respiratory, thoracic and mediastinal disorders: frequency not known: hiccups.

Paracetamol

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to paracetamol are rare and generally controlled by discontinuation of PARACETAMOL/TRAMADOL CIPLA, and

when necessary, symptomatic treatment. 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.
- Very rare cases of serious skin reactions have been reported.
- Metabolism and nutrition disorders: cases of pyroglutamic acidosis (PGA) were reported with frequency not known, when paracetamol is used alone or with concomitant treatment of flucloxacillin, especially in patients with risk factors and prolonged treatment (see **sections 4.4** and **4.5**).

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Accidental ingestion

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

Fatalities due to tramadol overdose have also been reported.

Signs and symptoms

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

Symptoms of overdose from tramadol

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

Symptoms similar to those of other centrally acting analgesics (opioids) are to be expected.

Symptoms of overdose from paracetamol

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours include gastrointestinal abnormality, pallor, nausea, vomiting, malaise, anorexia, diaphoresis and abdominal pain.

Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage. Paracetamol in massive overdosage may cause hepatic toxicity. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment for tramadol overdosage

A single or multiple overdose with PARACETAMOL/TRAMADOL CIPLA may be a potentially lethal polymedication overdose, and appropriate expert consultation, if available, is recommended.

While naloxone will reverse some, but not all symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Based on experience with tramadol, haemodialysis is not expected to be helpful in an overdose because it removes less than 7 % of the administered dose in a 4-hour dialysis period. Primary attention should be given to maintaining adequate ventilation and circulatory functions along with general supportive treatment.

Treatment for paracetamol overdosage

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 to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

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 / increased INR. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage. Administration should not be delayed while awaiting the results of the plasma assay. 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. Sodium chloride 0,9 % injection may be used where dextrose 5 % injection is unsuitable.

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 nomogram should be used after ingestion of PARACETAMOL/TRAMADOL CIPLA.

Monitor all patients with significant ingestions for at least 96 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.2.9. Other analgesics

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

ATC code: N02AJ13

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 ($V_{d,\beta}$=203 ± 40 l). It has a plasma protein binding of about 20 %. Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0,9 L/kg. A relatively small portion (~20 %) 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

Approximately 30 % of tramadol is excreted unchanged in the urine.

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.

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 sulpho-conjugate derivatives. 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

colloidal anhydrous silica

magnesium stearate

povidone

pregelatinised maize starch

sodium potato starch glycolate (Type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 ºC.

Store in a cool, dry place

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 4 aluminium/polyethylene strips of 15 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.

Building 9

Parc du Cap

Mispel Street

Bellville,

7530

Customer Care: 080 222 6662

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

First authorisation: 15 March 2022

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

26 March 2025