# PROFESSIONAL INFORMATION

## SCHEDULING STATUS

S5

## 1. NAME OF THE MEDICINE

PATRAM (film-coated tablets)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

Round, white to off-white, biconvex, film coated tablets, plain on both the surfaces.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

### 4.2 Posology and method of administration

**Posology**

To be used in adults and children over 16 years of age.

**DO NOT EXCEED THE RECOMMENDED DOSE.**

***Adults:***

For the management of pain, the recommended maximum single dose of PATRAM is 1 or 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. The lowest effective dose should be used for the shortest period of time.

A titration period of several days with gradual dose increases at the initiation of PATRAM therapy may be beneficial for some patients. It has been reported that patients with moderate to moderately severe chronic pain indicated that the tolerability of tramadol can be improved by starting tramadol at a low dose with gradual upward dose titration to reach doses that provide sufficient pain relief.

**Special populations**

*Children below 16 years of age*

The use of PATRAM is contraindicated in children below 12 years of age (see section 4.3).

The safety and effectiveness of PATRAM in children aged 12 to below 16 years of age has not been established (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use - Other risk factors for life-threatening respiratory depression in children).

*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*

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

*Hepatic impairment*

The use of PATRAM in patients with moderate to severe hepatic impairment is contraindicated.

**Method of administration:**

PATRAM tablets are for oral administration.

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

PATRAM can be administered without regard to food.

## 4.3 Contraindications

- PATRAM is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol, and other opioids such as codeine or to any of the other ingredients mentioned in section 6.
- PATRAM is also contraindicated in cases of acute intoxication with alcohol, hypnotics, other opioids or psychotropic medicines.
- Moderate to severe hepatic impairment.

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

- PATRAM must not be used for treatment of narcotic withdrawal.
- PATRAM should not be given to patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
- PATRAM should not be given to 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.
- PATRAM is can cause seizures (convulsions), hence it should not be used in patients with history of epilepsy or seizures of any cause (see section 4.4)
- PATRAM is contraindicated in all children younger than 12 years of age.
- PATRAM is contraindicated in children younger than 18 years of age following tonsillectomy and/or adenoidectomy

**4.4 Special warnings and precautions for use**

**PATRAM tablets 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.**

**The maximum dose of 8 tablets of PATRAM 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 medical practitioner (see section 4.9).**

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

**Seizures**

PATRAM 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 PATRAM 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 re-uptake 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, those with a history of seizures or in patients with a recognised risk for seizures e.g. drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramadol overdose.

***Anaphylactic reactions***

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

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 PATRAM) 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, Special warnings and precautions for use – Withdrawal).

***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 medicine, 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.

Even at labelled 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, Overdose - *Tramadol: symptoms and signs).*

***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, Contraindications). Because of the risk of life-threatening respiratory depression and death, avoid the use of PATRAM 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.

As with adults, when prescribing opioids for adolescents, healthcare 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, Posology and section 4.9, Overdose-Symptoms and signs, Tramadol).

**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. PATRAM should be used with caution and in reduced dosages when administered to patients receiving CNS depressants (see section 4.5, Interactions with other medicines and other forms of interaction).

***Drug dependence and potential for abuse***

Tramadol in PATRAM has a dependence potential and tolerance, psychic and physical dependence of the morphine- type (μ opioid) may develop with long-term use. The medicine has been associated with craving, drug- seeking behaviour and tolerance development. Cases of abuse and dependence on PATRAM have been reported. PATRAM should not be used in opioid-dependent patients.
PATRAM 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 PATRAM is not recommended.
PATRAM should not be given to patients who are suicidal or prone to addiction.
Caution should be advised in patients with a personal or family history of mental health disorders as tramadol in PATRAM has an increased risk for addiction and abuse.

***Hepatic impairment***

In patients with hepatic impairment the elimination of tramadol is delayed. In these patients, prolongation of the dosage intervals should be carefully considered according to the patient's requirements. Because of the presence of paracetamol, PATRAM should not be used in patients with moderate to severe hepatic impairment (see Section 4.3)

***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 PATRAM is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus, and unusual CNS symptoms have also been reported with abrupt discontinuation of tramadol hydrochloride. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the [medicine] medication dosages.

***Use with serotonergic medicines***

Use PATRAM with great caution in patients taking serotonergic medicines including SSRIs. Concomitant use of tramadol with serotonergic medicines including SSRI's increases the risk of adverse events, including seizure and serotonin syndrome (see section 4.5, Interaction with other medicines and other forms of interaction).

***Renal Impairment***

PATRAM has not been studied in patients with impaired renal function. Care is advised in the administration of paracetamol to patients with severe renal impairment. In patients with creatinine

clearances of less than 30 mL/min, it is recommended that the dosing interval of PATRAM be increased not to exceed 2 tablets every 12 hours.

Caution is advised if PATRAM 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.

***Serious skin reactions***

*Severe cutaneous adverse reactions (SCARs):*

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN);-acute generalised exanthematous pustulosis (AGEP); Stevens-Johnson syndrome (SJS); eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions, and if a patient develops SCARs, treatment with PATRAM must immediately be discontinued and appropriate treatment instituted.

***Hyponatraemia****:*

Hyponatraemia has been reported with the use of PATRAM usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medicines that may cause hyponatraemia. This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of PATRAM and appropriate treatment (e.g. fluid restriction). During PATRAM treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

***Precautions – general***

The recommended dose of PATRAM should not be exceeded.

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

## 4.5 Interaction with other medicines and other forms of interaction

***Concomitant use is contraindicated with:***

*Non-selective Monoamine oxidase (MAO) inhibitors*

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

In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with PATRAM.

• *Selective-A MAO Inhibitors*

Extrapolation from non-selective MAO inhibitors

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

• *Selective-B MAO Inhibitors*

Central excitation symptoms evocative of a 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 PATRAM

***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.

*Warfarin and anticoagulants*

*The paracetamol effect in PATRAM:*

- *Concurrent, chronic, high-dose administration of PATRAM may increase the anticoagulant effect. As medically appropriate, periodic evaluation of prothrombin time should be performed when PATRAM and warfarin-like compounds are administered concurrently.*

*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 medicines-such as selective serotonin re-uptake inhibitors (SSRIs) serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.2), tricyclic antidepressants and mirtazapine may cause serotonin toxicity.
  - Hepatotoxic medicines: Increased risk of hepatoxicity
  - Enzyme-inducing medicines: Increased risk of hepatoxicity and possible decrease in therapeutic effect of PATRAM.
  - Serotonin syndrome is likely when one of the following is observed:
  - Spontaneous clonus
  - Inducible or ocular clonus with agitation or diaphoresis,
  - Tremor and hyperreflexia
  - Hypertonia and body temperature > 38 °C and inducible or ocular clonus.
  - Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.
  - • Other opioid derivatives (including antitussive medicines and substitutive treatments) increased the risk of respiratory depression which can be fatal in cases of overdose.
  - Other central nervous system depressants, such as other opioid derivatives (including antitussive medicines and substitutive treatments), other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive medicines, thalidomide and baclofen.
  - These medicines can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
  - Sedating medicinal products such as benzodiazepines or related substances:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dose and duration of the concomitant use should be limited (see section 4.4).

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.

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

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

Ondansetron increased the requirement of tramadol in patients with post-operative pain.

- Caution is advised if PATRAM is administered concomitantly with flu-clloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients specially in patients with risks factors ( see section 4.4).

## 4.6 Fertility, pregnancy and lactation

***Pregnancy***

Safe use in pregnancy and lactation has not been established.

PATRAM is not recommended for pregnant mothers because tramadol has been shown to cross the placenta.

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

Prolonged use of PATRAM, or other opioids, during pregnancy may lead to neonatal opioid

withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.

***Lactation***

Safe use in lactation has not been established.

PATRAM is not recommended for lactating mothers because tramadol appears in breast milk

***Fertility***

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

**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.

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

**4.8 Undesirable effects**

***Tabulated list of adverse reactions***

| **System organ class** | **Adverse reaction** | **Frequency** |
|---|---|---|
| *Metabolism and nutrition disorders* | hypoglycaemia | Frequency unknown |
| | Weight increase | Less frequent |
| | Pyroglutamic aciduria (5-oxoprolinuria) | Frequency Unknown |

| | | |
|---|---|---|
| | and high-anion gap metabolic acidosis | |
| *Psychiatric disorders* | Medicine dependence | Frequency unknown |
| | confusion, mood altered, anxiety, nervousness, euphoria, sleep disorders, anorexia, amnesia , insomnia | Frequent |
| | depression, hallucinations, depersonalisation , nightmares, delirium, drug dependence, drug abuse, | Less frequent |

| | | |
|---|---|---|
| | emotional lability, hallucinations, impotence, bad dreams, abnormal thinking | |
| *Nervous system disorder* | dizziness, somnolence, headache, trembling, | Frequent |
| | involuntary muscle contractions, paraesthesia, amnesia, ataxia, convulsions, stupor, syncope, vertigo, speech disorders, hypertonia, migraine, | Less frequent |

| | | |
|---|---|---|
| *Eye disorders:* | abnormal vision, vision blurred, miosis, mydriasis | Less frequent |
| *Ear and labyrinth disorders:* | tinnitus | Less frequent |
| *Blood disorders and Lymphatic disorders* | anaemia, prothrombocytopenia, leucopenia, pancytopenia, neutropenia and agranulocytosis. | Less frequent |
| *Cardiac disorders:* | palpitations, tachycardia, dysrhythmia, syncope | Less frequent |
| *Gastro-intestinal disorders:* | Nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence | Frequent |

| | | |
|---|---|---|
| | dysphagia, melaena, tongue oedema. | Less frequent |
| *General disorders and administration site conditions* | asthenia, fatigue, hot flushes | Frequent |
| | chills, chest pain, rigors, syncope and withdrawal syndrome | Less frequent |
| *Investigations:* | Transaminases increased | Less frequent |
| *Renal and urinary disorders* | albuminuria, micturition disorders (dysuria and urinary retention), oliguria, renal failure | Less frequent |
| *Respiratory, thoracic and mediastinal disorders* | dyspnoea | Less frequent |

| | | |
|---|---|---|
| *Skin and subcutaneous tissue disorders* | hyperhidrosis, pruritus | Frequent |
| | dermal reactions (e.g. rash, pruritis, urticaria), increased sweating | Less frequent |
| *Vascular disorders:* | hypertension, aggravated hypertension, hypotension | Less frequent |
| **Post marketing experience** | | |
| *Gastro-intestinal disorders:* | Increased risk of abdominal pain, including pancreatitis | Less Frequent |
| *Skin and subcutaneous tissue disorders* | Erythema, flushing, acute generalised | Frequency unknown |

| | | |
|---|---|---|
| | exanthematous, pustulosis<br>Toxic epidermal necrolysis<br>Stevens-Johnson syndrome<br>Risk of Fixed drug eruptions (FDE)<br>Risk of Drug-induced hypersensitivity syndrome (DIHS). | |
| *Renal and urinary disorders* | albuminuria, micturition disorders (dysuria and urinary retention) | Frequency unknown |

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 (tramadol).

***Clinically significant adverse experiences reported post-marketing with tramadol hydrochloride include:***

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

Serotonin syndrome (symptoms may include fever, excitation, shivering and agitation) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAO-inhibitors. Post-marketing surveillance of tramadol has revealed alterations of warfarin effect, including elevation of prothrombin/INR times.
Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.

***Clinically significant adverse experiences reported post-marketing with paracetamol include:***

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

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorisation of PATRAM is important. It allows continued monitoring of the benefit/risk balance of PATRAM. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000.

## 4.9 Overdose

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

***Tramadol***

The initial symptoms of tramadol overdosage may include respiratory depression and/or seizures. Primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all symptoms caused by overdosage, the risk of seizures is also increased with naloxone administration. Treatment of restlessness and / or convulsions is symptomatic and supportive (benzodiazepines/ barbiturates).

Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with PATRAM with haemodialysis or haemofiltration alone is therefore not suitable for detoxification.

***Paracetamol***

Prompt treatment is essential. In the event of an overdosage, consult a medical practitioner immediately, or take the person to a hospital directly. A delay in starting treatment may mean that

antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed. Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicine that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of prothrombin time.

Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage.

Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

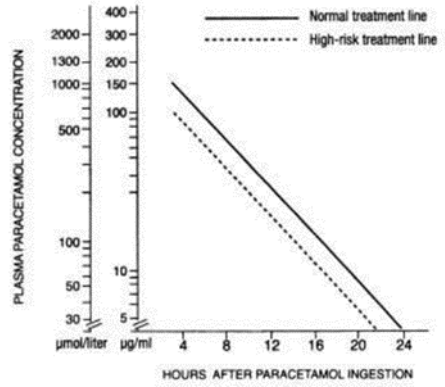
*Treatment for paracetamol overdosage:*

*N*-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N -acetylcysteine in 200 mL dextrose injection given intravenously over 15 minutes, followed

by an infusion of 50 mg/kg in 500 mL dextrose injection over the next four hours, and then 100 mg/kg in 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 overdose nomogram.




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

Monitor all patients with significant ingestions for at least ninety six hours.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A.2.9. Other analgesics.

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

ATC code: N02AJ13.

Tramadol is a centrally acting synthetic analgesic compound whose analgesic profile can be attributed to the binding of parent and *O*-demethylated (M1) metabolite to μ-opioid receptors as well as the weak inhibition of neuronal re-uptake of noradrenaline and serotonin. Paracetamol also has centrally acting analgesic effects.

### 5.2 Pharmacokinetic properties

***Absorption***

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

***Distribution***

Tramadol has a high tissue affinity ($V_{d,\ \beta}$ = 203 ± 40 L). It has a plasma protein binding of about 20 %.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0,9 L/kg. A relative small portion (~20 %) of paracetamol is bound to plasma proteins.

***Metabolism***

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

***Elimination***

Approximately 30 % of tramadol is excreted unchanged in the urine. Tramadol and its metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of tramadol and its M1 metabolite are approximately 6 and 7 hours respectively. Paracetamol is eliminated from the body primarily by formation of glucuronide and sulphate conjugates in a dose-dependent manner. The half-life of paracetamol is about 2 – 3 hours in adults. Less than 9 % of paracetamol is excreted unchanged in the urine.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

***Core tablet:***

Pregelatinized starch (Starch 1500)

Maize starch

Sodium starch glycolate (Type A)

Colloidal silicon dioxide (Aerosil 200)

Magnesium stearate

***Film-coating:***

*Opadry White# (Y-1-7000) consisting of:*

Hypromellose

Titanium dioxide

Polyethylene glycol

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months

Store at or below 25 °C. Protect from light.

### 6.4 Special precautions for storage

Store at or below 25 °C.

Keep the tablets in the original container until required for use.

### 6.5 Nature and contents of container

Clear transparent PVC/PVDC - Aiuminium blister strip of 10 tablets

Pack Sizes(s): 10 x 10's or 6 x 10's tablets per carton – packed in outer carton.

### 6.6 Special precautions for disposal and other handling

No special requirements

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext.1, Roodepoort

Johannesburg

1724

Telephone: +27(0) 12 643 2000

## 8. REGISTRATION NUMBER

46/2.9//0449

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 November 2016

## 10. DATE OF REVISION OF THE TEXT

04 February 2026

| **Namibia:** |
| --- |
| 17/2.9/0121 |