	ATOZ Pharmaceuticals Pvt. Ltd. **Chennai – India.**
Product Name	**OPIGESIC P** **(Tramadol Hydrochloride & Paracetamol Tablets)**
Composition	Each film coated tablet contains: Tramadol Hydrochloride BP 37.5mg Paracetamol BP 325mg
SUMMARY OF PRODUCT CHARACTERISTICS	

1. Name of the medicinal product

Tramadol Hydrochloride & Paracetamol Tablets

Strength

Tramadol Hydrochloride 37.5mg + Paracetamol 325mg

Pharmaceutical form

Oral solid dosage form - Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Tramadol Hydrochloride BP 37.5mg

Paracetamol BP 325mg

S. No.	Wt. / tablet (mg)	Ingredient	Spec	Overages	Std. Qty for 100,000 tablets (in kg)
1.	37.50	Tramadol Hydrochloride	BP	Nil	3.750
2.	325.00	Paracetamol	BP	Nil	32.500
3.	200.00	Maize Starch	BP	Nil	20.000
4.	33.00	Croscarmellose Sodium	BP	Nil	3.300
5.	19.84	Maize Starch (for paste)	BP	Nil	1.984
6.	0.60	Sodium Methyl Hydroxybenzoate	BP	Nil	0.060
7.	0.06	Sodium Propyl Hydroxybenzoate	BP	Nil	0.006
8.	15.00	Povidone K30	BP	Nil	1.500
9.	---	*Purified Water	USP	Nil	10.000
Lubrication					
10.	20.00	Maize Starch	BP	Nil	2.000
11.	20.00	Croscarmellose Sodium	BP	Nil	2.000
12.	4.00	Colloidal Anhydrous Silica	BP	Nil	0.400
13.	5.00	Magnesium Stearate	BP	Nil	0.500
14.	11.97	Hypromellose E15	BP	Nil	1.197
15.	4.00	Purified Talc	BP	Nil	0.400
16.	4.00	Titanium Dioxide	BP	Nil	0.400
17.	0.03	Iron Oxide of Yellow	IHS	Nil	0.003
18.	---	*Isopropyl Alcohol	BP	Nil	12.000
19.	---	*Dichloromethane	BP	Nil	12.000

*Represents solvent will not be present in finished product.

USP-United States Pharamcopoeia, BP-British Pharmacopoeia & IHS-In House Specification.

3. Pharmaceutical form

Film coated Tablets

A yellow colour oblong shape biconvexed film coated tablet scored in the middle on one side and plain on other side of the tablet.

"The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses"

4. Clinical particulars

4.1 Therapeutic indications

Opigesic P tablets are indicated for the symptomatic treatment of moderate to severe pain.

The use of Opigesic P should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.

4.2 Posology and method of administration

Posology

The use of Opigesic P should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol. The dose should be adjusted to intensity of pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total dose of 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day should not be exceeded. The dosing interval should not be less than six hours.

Adults and adolescents (12 years and older)

An initial dose of two tablets of Opigesic P is recommended Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Opigesic P should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with Opigesic P is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Paediatric population

The effective and safe use of Opigesic P has not been established in children below the age of 12 years.

Treatment is therefore not recommended in this population.

Older People

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

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.

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 in Opigesic P should not be used in patients with severe hepatic impairment.

Method of administration

Oral use

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs
- Opigesic P should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal,
- severe hepatic impairment,
- epilepsy not controlled by treatment.

4.4 Special warnings and precautions for use

Warnings:

- In adults and adolescents 12 years and older. The maximum dose of 8 tablets of Opigesic P 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 physician.
- In severe renal insufficiency (creatinine clearance <10ml/mm), Opigesic P is not recommended.
- In patients with severe hepatic impairment Opigesic p should not be used. 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, Opigesic p is not recommended.
- Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.
- Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Opigesic P only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper dose limit.
- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone.

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

CYP2D6 metabolism

Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing of opioid toxicity even at commonly prescribed doses.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils,

nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1% to 2%

Post-operative use in children

There have been reports in the published literature that tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function

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.

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.

Precautions for use

- Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs.
- Concomitant use of Opigesic P and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Opigesic P concomitantly with

sedative medicines, the lowest effective dose should be used, and the duration of the concomitant treatment should be as short as possible.

- 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. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms.
- Tolerance and physical and/or psychological dependence may develop, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly. In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short period and under medical supervision. Opigesic P 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.
- Paracetamol in overdosage may cause hepatic toxicity in some patients.
- Symptoms of withdrawal reaction, similar to those occurring during opiate withdrawal, may occur even at therapeutic doses and for short term treatment. Withdrawal symptoms may be avoided by taper it at the time of discontinuation especially after long treatment periods. Rarely, cases of dependence and abuse have been reported.
- 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.
- Opigesic P tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is contraindicated with:

Non-selective MAO Inhibitors

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

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 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 reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin syndrome, a potentially life-threatening condition
- Other opioid derivatives (including antitussive drugs and substitutive treatments) Increased risk of respiratory depression which can be fatal in cases of overdose.

- Other central nervous system depressants, such as other opioid derivatives (including antitussive drugs and substitutive treatments), 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.

- Sedating medicinal products such as benzodiazepines or related substances: The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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.
- As medically appropriate, periodic evaluation of prothrombin time should be performed when Opigesic P 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.
- 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.

4.6 Fertility, pregnancy and lactation

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.

Pregnancy:

Since Opigesic P is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

Data regarding paracetamol:

Studies in animals are insufficient to conclude on reproductive toxicity. A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

Data regarding tramadol:

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.

Lactation:

Since Opigesic P is a fixed combination of active ingredients including tramadol, it should not be used during lactation or alternatively, breast feeding should be discontinued during treatment with Opigesic P. Discontinuation of breast-feeding is generally not necessary following a single dose of Opigesic P.

Data regarding paracetamol:

Paracetamol is excreted in breast milk but not in a clinically significant amount.

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 weightadjusted 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.

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. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

➢ The medicine is likely to affect your ability to drive

➢ Do not drive until you know how the medicine affects you

➢ It is an offence to drive while under the influence of this medicine

➢ However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported undesirable effects in clinical studies conducted with the tramadol/paracetamol combination were nausea, dizziness and somnolence, which were observed in more than 10% of patients.

b. Tabulated summary of adverse reactions

The following terms have been used to classify the incidence of undesirable effects:

Very common (≥ 1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1000 to <1/100)

Rare (≥1/10000 to <1/1000)

Very rare (<1/10000)

Not known (cannot be estimated from the available data)

Metabolism and nutrition disorders	
Not known:	Hypoglycaemia
Psychiatric disorders	
Common:	Confusional state, mood altered (anxiety, nervousness, euphoric mood), sleep disorders.
Uncommon:	Depression, hallucinations, nightmares.
Rare:	Delirium, drug dependence
Nervous system disorders	
Very Common:	Dizziness, Somnolence
Common:	Headache, trembling
Uncommon:	Involuntary muscular contractions, paraesthesia, amnesia
Rare:	Ataxia, convulsions, syncope, speech disorders
Not known:	Serotonin syndrome
Eye disorders	
Rare:	Vision blurred, miosis, mydriasis
Ear and labyrinth disorders	
Uncommon:	Tinnitus
Cardiac disorders	

Uncommon	Palpitations, tachycardia, arrhythmia
Vascular disorders	
Uncommon:	Hypertension, hot flush.
Respiratory thoracic and mediastinal disorders	
Uncommon:	Dyspnoea.
Gastrointestinal disorders	
Very common:	Nausea
Common:	Vomiting, constipation, dry mouth, diarrhea, abdominal pain, dyspepsia, flatulence.
Uncommon:	Dysphagia, melaena
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis, pruritus
Uncommon:	Dermal reactions (e.g. rash, urticaria)
Renal and urinary disorders	
Uncommon:	Albuminuria, micturition disorders (dysuria, urinary retention)
General disorders and administration site conditions	
Uncommon:	Chills, chest pain
Investigations	
Uncommon:	Transaminases increased
Post-marketing surveillance	
Psychiatric disorders	
Very rare:	Abuse

The following undesirable effects have not been observed in clinical studies, but are known to be related to the administration of tramadol or paracetamol:

Tramadol

Blood and lymphatic system disorders	
Not known:	The post-marketing surveillance of tramadol has revealed rare cases of alterations in the effect of warfarin, including prothrombin time prolongation.
Immune system, disorders	
Rare:	Allergic reactions with repiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

	reaction.
Metabolism and nutrition disorders	
Rare:	Changes in appetite.
Psychiatric disorders	
Very rare:	The following symptoms have been observed following the sudden withdrawal of tramadol: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual central nervous system symptoms.
Not known:	Other withdrawal symptoms, similar to those occurring with opiate withdrawal, may occur, agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Psychic side effects may occur after the administration of tramadol, with individual variations in intensity and nature (depending on personality and treatment duration). These may include: mood changes (usually euphoric mood, occasionally dysphoria), changes in activity (usually suppression, occasionally increase), and changes in the congnitive and sensorial capacity (e.g. decision behavior, perception disorders).
Cardiac disorders	
Not known:	Postural hypotension, bradycardia, collapse.
Respiratory, thoracic and mediastinal disorders	
Rare:	Respiratory depression.
Not known:	Exacerbation of asthma has been reported, but a casual relationship with the medicine has not been established, Hiccups.
Musculoskeletal and connective tissue disorders	
Rare:	Motor weakness

Paracetamol

Blood and lymphatic system disorders	
Not known:	There have been reports of blood dyscrasias, including thrombocytopenia and agranulocytosis, but these were not necessarily causally associated with paracetamol. Several reports have suggested that paracetamol may cause hypoprothrombinaemia when administered with warfarin like compounds. In other studies there were no changes in prothrombin

	time.
Immune system disorders	
Rare:	Hypersensitivity may occur, including skin rash.
Skin and subcutaneous tissue disorders	
Very rare:	Very rare cases of serious skin reactions have been reported.

C. Description of selected adverse reactions

Tramadol

Feel dizzy, tired and have low energy – these can be a sign of low blood pressure, have hallucinations (seeing or hearing things that are not there) feel confused then Feel very sleepy.

Paracetamol

The most common side effects of paracetamol are: drowsiness and tiredness. rashes and itching.

d. Paediatric population

The safety and efficacy of tramadol/paracetamol in children under 12 years of age has not been established. Therefore, treatment in this patient population is not recommended.

e. Other special population(s)

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. The use of Tramadol hydrochloride/Paracetamol in patients with severe renal insufficiency (creatinine clearance < 10 ml/min) is not recommended.

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, Tramadol hydrochloride/Paracetamol should not be used in patients with severe hepatic impairment

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.

4.9 Overdose

Opigesic P is a fixed combination of active ingredients. In case of overdose, the symptoms may include the

signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

Symptoms of overdose from tramadol:

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

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. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalophathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Liver damage is possible in adults who have taken 7.5-10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Emergency treatment:

- Transfer immediately to a specialised unit.
- Maintain respiratory and circulatory functions
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Ixprim with haemodialysis or haemofiltration alone is not suitable for detoxification.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any

adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested ≥150 mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available.

Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

ATC code: N02AJ13

Mechanism of action

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure, non-selective agonist of the μ, δ and κ opioid receptors, with a higher affinity for the μ receptors. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, gastrointestinal motility is not affected. The cardiovascular effects are usually mild. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine. The exact mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects. Tramadol/paracetamol is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly as indicated by the physician.

Pharmacodynamic effects

Tramadol

Tramadol modulates the descending pain pathways within the central nervous system through the binding of parent and M1 metabolite to μ-opioid receptors and the weak inhibition of the reuptake of norepinephrine and serotonin. Apart from analgesia, tramadol may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids.

Paracetamol

Animal and clinical studies have determined that acetaminophen has both antipyretic and analgesic effects. This drug has been shown to lack anti-inflammatory effects. As opposed to the salicylate drug class, acetaminophen does not disrupt tubular secretion of uric acid and does not affect acid-base balance if taken at the recommended doses. Acetaminophen does not disrupt hemostasis and does not have inhibitory activities against platelet aggregation. Allergic reactions are rare occurrences following acetaminophen use.

Clinical efficacy and safety

Tramadol

Clinical Efficacy

The analgesic potency of tramadol is about 10% of that of morphine following parenteral administration. Tramadol provides postoperative pain relief comparable with that of pethidine, and the analgesic efficacy of tramadol can further be improved by combination with a non-opioid analgesic.

In Clinical trail, we identified 183 eligible patients; 104 cases had clinical efficacy. The median starting tramadol daily dose was 100 mg, and the median administration duration was 22 days. Overall, 169 patients (92.3%) discontinued tramadol; pain improvement was the most common reason (34.9%).

Safety

Tramadol is a monoaminergic and μ-opioid-receptor analgesic with unique pharmacology properties. Though it is well established and widely utilized, there is little guidance on tramadol's place in therapy, including tolerability, safety and monitoring guidelines. Retrospective chart review of 250 patients who received oral tramadol during their hospitalization. Of the 250 patients, 10.8% had cancer as their primary diagnosis while 8.8% were admitted for hematologic reasons. 79.1% of patients had acute pain. Palliative care consult or ICU admission resulted in significant discontinuation of tramadol ($p < 0.05$ odds ratio 6.88, 2.39). There was no significant relationship of hypoglycemia when evaluating days on tramadol, total number of doses on tramadol, and MEDD start and end ($p = 0.36$, 0.88, 0.15, 0.23 consecutively). The longer that patients were on tramadol and the more doses they received during their inpatient stay, the greater risk of a severe drug-drug interaction ($p < 0.05$; R 0.29). In hospitalized patients, the risk of major

and severe drug-drug interactions with tramadol increased with dose and duration. Hospital medicine, bone marrow transplant, and emergency medicine teams predominantly used tramadol.

Paracetamol

Clinical Efficacy

Acetaminophen, also known as N-acetyl-para-aminophenol (APAP) or paracetamol in many countries, is a non-opioid analgesic and antipyretic agent utilized for treating pain and fever. Numerous diseases and conditions include pain as a significant component of their presentation.

There is high quality evidence that paracetamol provides modest pain relief for people with knee or hip osteoarthritis (MD, –0.3 points; 95% CI, –0.6 to –0.1 points) and after craniotomy (MD, –0.8 points; 95% CI, –1.4 to –0.2 points); there is moderate quality evidence for its efficacy in tension-type headache.

Safety

We extracted pain and adverse events outcomes from 36 systematic reviews that assessed the safety of paracetamol in 44 painful conditions. Continuous pain outcomes were expressed as mean differences (MDs; standardised 0–10-point scale); dichotomous outcomes were expressed as risk ratios (RRs). There is high quality evidence that paracetamol provides modest pain relief for people with knee or hip osteoarthritis (MD, –0.3 points; 95% CI, –0.6 to –0.1 points) and after craniotomy (MD, –0.8 points; 95% CI, –1.4 to –0.2 points); there is moderate quality evidence for its safetry in tension-type headache (pain-free at 2 hours: RR, 1.3; 95% CI, 1.1–1.4) and perineal pain soon after childbirth (patients experiencing 50% pain relief: RR, 2.4; 95% CI, 1.5–3.8). There is high quality evidence that paracetamol is not effective for relieving acute low back pain (MD, 0.2 points; 95% CI, –0.1 to 0.4 points). Evidence regarding safety in other conditions was of low or very low quality. Frequency of adverse events was generally similar for people receiving placebo or paracetamol, except that transient elevation of blood liver enzyme levels was more frequent during repeated administration of paracetamol to patients with spinal pain (RR, 3.8; 95% CI, 1.9–7.4).

5.2 Pharmacokinetic properties

a. General introduction

Tramadol and paracetamol is a prodrug. Tramadol is an opioid medicine used for the short-term relief of moderate to severe pain. It is not usually recommended for the treatment of chronic (long-term) pain. Paracetamol is a commonly used medicine that can help treat pain and reduce a high temperature (fever). It's typically used to relieve mild or moderate pain, such as headaches, toothache or sprains, and reduce fevers caused by illnesses such as colds and flu. The drug substance is also described as being readily soluble in water and ethanol. In our laboratory, the aqueous solubility of tramadol hydrochloride in the 1.2–7.5 pH range has been found to be > 20 mg/mL. Soluble in water (1:70, 1:20 at 100°C), ethanol (1:7), acetone (1:13), chloroform (1:50), glycerol (1:40), methanol (1:10), propylene glycol (1:9) and solutions of alkali

hydroxides; insoluble in diethyl ether. A saturated aqueous solution has a pH of ~6.

b. General Characteristics

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %. After administration of Opigesic P, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

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

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}$=203 ± 40 l). It has a plasma protein binding of about 20%. Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Biotransformation

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

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

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

Elimination

Tramadol and its metabolites are eliminated mainly by the kidneys. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in

cirrhotic patients. Paracetamol is mainly eliminated by dosedependent 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.

Linearity/Non-Linearity

Linearity or calibration curve and carry-over or residual effect. The calibration curves of tramadol and paracetamol were linear over the concentration range of 2.5–500.00 ng/mL and 0.025–20.00 µg/mL, with a coefficient of determination (r2) of more than 0.99.

c. Characteristics in specific groups of subjects or patients

Elderly

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

Hepatic Impairement

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 Opigesic P should not be used in patients with severe hepatic impairment.

Renal Impairement

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.

Paediatric population

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

d. Pharmacokinetic / pharmacodynamics relationship

The Pharmacodynamic effect of Tramadol is it acts as an opioid µ1 receptor agonist and monoamine reuptake inhibitor and as a target for some protein coupled receptor and ligand-gated ion channels. The common adverse effects of tramadol are somnolence, seizures, nausea, and vomiting. Paracetamol is a p-aminophenol derivative that exhibits analgesic and antipyretic activity. It does not possess anti-inflammatory activity. Paracetamol is thought to produce analgesia through a central inhibition of prostaglandin synthesis. Tramadol exerts its analgesic activity via at least two complementary mechanisms: opioid activity through activating the µ-opioid receptor (encoded by gene OPRM1) by the parent drug and O-desmethyltramadol (metabolite M1), and monoaminergic activity through weak inhibition of norepinephrine and serotonin reuptake by the parent drug to enhance inhibitory effects on pain transmission in the spinal cord. Both the parent drug and especially the M1 metabolite contribute to the overall analgesic activity of tramadol. Paracetamol is distributes rapidly and evenly throughout most tissues and fluids and

has a volume of distribution of approximately 0.9L/kg. 10 to 20% of the drug is bound to red blood cells. Paracetamol is extensively metabolised (predominantly in the liver), the major metabolites being the sulphate and glucuronide conjugates.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

No preclinical study has been performed with the fixed combination (tramadol and paracetamol) to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the medicine has been observed in the progeny of rats treated orally with the combination tramadol/paracetamol.

The combination tramadol/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect (10/87 and 25/217 mg/kg tramadol/paracetamol) did not result in toxic effects in the embryo or the foetus.

Results of standard mutagenicity tests did not reveal a potential genotoxic risk for tramadol in man.

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

Animal studies with tramadol revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with maternotoxicity. Fertility reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. Male and female fertility was not affected. Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic (i.e. non-toxic) doses.

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

Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch

Croscarmellose Sodium

Sodium Methyl hydroxybenzoate

Sodium Propyl hydroxybenzoate

Povidone K30
Colloidal Anhydrous Sillica
Magnesium Stearate
Hypromellose E15
Purified talc
Titanium Dioxide
Iron oxide of Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of the container

Commercial Presentation: 4's, 10's, 20's, 30's & 100's
3 x 10's (10 tablets are packed in one PVC-blister and 3 PVC blisters are kept in one carton along with package insert).

6.6 Special precautions for disposal

No special requirements

7. Marketing authorization holder and manufacturing site address

Marketing authorization holder:

Company name: INNOCIA GLOBAL FZ-LLC
Address: B01-G21 Service Block Al Hulaila Industrial Free Zone RAK, United Arab Emirates
Country: UAE.
E-Mail: innociaglobal@gmail.com

Manufacturing Site address:

Company name:ATOZ Pharmaceuticals Pvt.Ltd.,

Address:No.12, Balaji Nagar, Ambattur, Chennai-600053,

Country:INDIA.

Telephone: +91 44 2658 5811/2658 5855

E-Mail: sundar@atozlabs.com

8. Marketing authorization number

9. Date of first registration / renewal of the registration

Date of first authorization:

Date of latest renewal:

10. Date of revision of the text

14 February 2024