For the Use of a Registered Medical Practitioner Only

Warning:
Taking more than daily dose of Paracetamol may cause serious liver damage or allergic reactions (eg. swelling of the face, mouth and throat, difficulty in breathing, itching or rash).

1. **GENERIC NAME**
   Paracetamol and Tramadol Tablets I.P.
   Acuvin™

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   Each Film Coated Tablet Contains:
   Paracetamol I.P……..…..325 mg
   Tramadol Hydrochloride I.P…….37.5 mg
   Colours: Yellow Oxide of Iron & Titanium Dioxide I.P.

3. **DOSAGE FORM AND STRENGTH**
   Kindly refer to section 1 & 2

4. **CLINICAL PARTICULARS**
   4.1 THERAPEUTIC INDICATION
   Indicated for severe acute pain only for a period not exceeding 5 days.

   4.2 POSOLOGY AND METHOD OF ADMINISTRATION
   Acuvin is taken orally with or without food.

   Usual Adult Dose for Pain
   Usual dose: 2 tablets every 4 to 6 hours as needed for pain
   Maximum dose: 8 tablets per day
   Maximum duration: 5 days

   For the short-term management of acute pain; use should be limited to 5 days or less.
   In case of a missed dose, skip the missed dose and go back to regular dosing schedule. 2 doses should not be taken at once.

   Usual Geriatric Dose for Pain

   Caution needs to be practiced due to potential for greater sensitivity to adverse events.

   Renal Dose Adjustments

   CrCl less than 30 mL/min: Dosing interval increased to every 12 hours.
   Maximum dose: 4 tablets per day.

Liver Dose Adjustments

Use is not recommended.

4.3 CONTRAINDICATIONS

The drug is contraindicated in:

- Patients with known hypersensitivity to any of the components or any other codeine- or morphine-related medicine (eg, oxycodone, hydrocodone, dihydrocodeine, hydromorphone
- Known hypersensitivity to opioids.
- Acute intoxication with alcohol, analgesics, hypnotics, opioids or psychotropic drugs.
- Subjects who are receiving MAO inhibitors or who have taken them within the last 14 days.
- Patients with uncontrolled epilepsy or epilepsy not adequately controlled by treatment.
- Pregnancy
- Lactation
- Active peptic ulcer or GI bleeding
- History of allergic responses to aspirin or other NSAIDs
- Acute porphyria
- Blood coagulation impairment
- Tramadol must not be used for narcotic withdrawal treatment
- Patient is already taking carbamazepine, sodium oxybate (GHB)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should consult a physician prior to use.

Acute abdominal conditions

The administration of tramadol may complicate the assessment of patients with acute abdominal conditions.

Respiratory depression

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

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

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

Renal and hepatic disease

With the prolonged half-life in these conditions, steady state achievement is delayed, so that it may take several days for elevated plasma concentrations to develop.

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 (see sections 4.5, 4.8 and 4.9).
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.

Renal disease
In patients with renal insufficiency the tramadol elimination is delayed. In cases of severe renal insufficiency tramadol is not recommended.

Hepatic disease
Metabolism of tramadol and M1 is reduced in patients with advanced liver cirrhosis. In cirrhotic patients, dosage reduction is recommended.

Patients physically dependent on opioids
Tramadol is not recommended as a substitute in opioid-dependent patients. In patients with a tendency for drug abuse or dependence, treatment with tramadol should only be carried out for short periods under strict medical supervision.

Seizure risk
Convulsions are reported in patients receiving tramadol. The risk is increased when doses of tramadol exceed the recommended upper daily dose limit Patients with epilepsy or the ones susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

Anaphylactoid reactions
Serious and rarely fatal anaphylactoid reactions have been reported in patients taking tramadol. These reactions often occur after the first dose. Other reported reactions include pruritus, bronchospasm, hives and angioedema.

Long-term use
When long term tramadol treatment is required, careful and regular monitoring should be carried out to establish whether, and to what extent, ongoing treatment is necessary.

Labour and delivery

The use of tramadol in pregnant women prior to or during labour is not recommended unless the potential benefits outweigh the risks, because safe use in pregnancy has not been established. Chronic use during pregnancy may cause neonatal withdrawal symptoms. If tramadol were to be used during labour, it may lead to respiratory depression in the new-born.

Sleep-related breathing disorders:
Opioids can cause sleep-related breathing disorders including central sleep apnoea (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.

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.

Warning: Tramadol should be used for severe acute pain only for a period not exceeding 5 days.

4.5 DRUGS INTERACTIONS

Drug	Drug Interaction	Remarks
CNS depressants	The combination of tramadol with mixed opiate agonists/antagonists (eg. buprenorphine, pentazocine) is not advisable because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.	Tramadol should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anaesthetic agents, phenothiazines, tranquillisers or sedative hypnotics.
Serotonergic agents	Concomitant therapeutic use of tramadol and serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclics antidepressants and mirtazapine may cause serotonin toxicity.	
Coumarin derivatives	Concomitant use may increase international normalised ratio (INR) with	Caution should be exercised during concomitant treatment with tramadol and coumarin

	major bleeding and ecchymoses in some patients.	derivatives (eg. warfarin)
Drugs which reduce the seizure threshold	Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure-threshold-lowering drugs (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.	
MAO inhibitors	Tramadol inhibits the uptake of noradrenaline and serotonin.	Tramadol should not be used in patients who are taking MAO inhibitors or who have taken them within the last fourteen days.
Carbamazepine	Concomitant administration of tramadol with carbamazepine causes a significant increase in tramadol metabolism, presumably through metabolic induction by carbamazepine.	Patients receiving chronic carbamazepine doses of up to 800 mg daily may require up to twice the recommended dose of tramadol.
Quinidine, phenothiazines, antipsychotic agents	Drugs that selectively inhibit that isoenzyme may cause increased concentrations of tramadol and decreased concentrations of M1.	
Probenecid	Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.	
Chloramphenicol	Paracetamol may increase chloramphenicol concentrations.	
Alcohol and anticonvulsant agents	The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver	

	microsomal enzymes such as alcohol and anticonvulsant agents.	
Gastric emptying drugs	Paracetamol absorption is decreased by substances that decrease gastric emptying,	
Colestyramine	Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.	
Anticoagulant / Antiplatelet drugs		Dosage may require reduction if used concomitantly with paracetamol for a prolonged period of time.
Interaction with other medicinal products and other forms of interaction		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

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy:
Since this medicine is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

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

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

Breast-feeding:
Since this medicine is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

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

Data regarding tramadol:
Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

Pediatric population:
The effective and safe use of Tramadol hydrochloride/Paracetamol has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to its sedative effect, patients should be advised to avoid driving or operating machinery whilst taking tramadol.

4.8 UNDESIRABLE EFFECTS

Immune system disorders	Anaphylaxis, allergic reactions, shock reactions
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatraemia secondary to decreased free-water excretion
Metabolism and nutrition disorders	Changes in appetite
Psychiatric	Hallucinations, confusional state, sleep disturbance, anxiety,

disorders	nightmares, delirium, changes in mood (usually euphoric mood, occasionally dysphoria), changes in activity (usually suppression, occasionally increase), changes in cognitive and sensorial capacity (eg. decision behaviour, perception disorders), Drug dependence and abuse (Rare)
Nervous system disorders	Dizziness Autonomic nervous effects (mainly dry mouth, perspiration), sedation, asthenia, headache Trembling Speech disorders, paraesthesia, coordination disturbance, seizures, involuntary muscle contractions, syncope, tremor. Not known: Serotonin syndrome, Tramadol associated Hiccups
Eye disorders	Mydriasis, visual disturbance (blurred vision), miosis
Cardiac disorders	Flushing, tachycardia Bradycardia
Vascular disorders	Orthostatic dysregulation (tendency to collapse and cardiovascular collapse)
Respiratory, thoracic and mediastinal disorders	Dyspnoea, respiratory depression (when the recommended doses are considerably exceeded and other respiratory depressant substances are administered concomitantly) Worsening of asthma (causality not established), Hiccups
Gastrointestinal disorders	Nausea Constipation,vomiting Diarrhoea, flatulence, urge to vomit, abdominal pain, dyspepsia
Hepatobiliary disorders	Elevated liver enzymes
Skin and subcutaneous tissue disorders	Sweating Rash, skin reactions, pruritus, Paracetamol associated Fixed Drug Eruption (FDE)
Musculoskeletal and connective tissue disorders	Motor system weakness
Renal and urinary disorders	Dysuria, micturition disorders (difficulty in passing urine and urinary retention)
General disorders and administration site conditions	Fatigue

4.9 OVERDOSAGE

Symptoms of overdosage with tramadol are resemble those of other centrally acting analgesics (opioids) and include vomiting, miosis, cardiovascular collapse, consciousness disorders including coma, convulsions, respiratory depression and respiratory arrest. Serotonin syndrome has also been reported.

- If overdosage occurs, general emergency measures should be implemented.
- Keeping the respiratory airways open, maintain respiration and circulation.
- If overdosage is due to ingestion, emptying the stomach by gastric lavage should be considered. Activated charcoal may reduce absorption of the drug if given within 1-2 hours after ingestion.
- In patients who are not fully conscious or have impaired gag reflex, activated charcoal should be administered via a nasogastric tube, once the airway is protected.
- Naloxone may reverse respiratory depression, but not all symptoms caused by overdosage with tramadol.
- Tramadol is minimally eliminated from the serum by hemodialysis or hemofiltration. Therefore treatment of overdosage with tramadol with haemodialysis or haemofiltration alone is not suitable for detoxification.

Gastric Decontamination/Prevention of Absorption of Paracetamol

Gastric decontamination should be carried out according to standard treatment guidelines.
a) Activated charcoal should be given during the immediate post ingestion period, especially in the case of a mixed drug overdose. Although there are no data to support the efficacy of activated charcoal beyond 2 hours, it is reasonable to administer activated charcoal for up
to 4 hours post-ingestion. Administration of activated charcoal will not interfere with subsequent administration of oral acetylcysteine therapy.
b) Syrup of ipecac given to children during the prehospital phase may reduce subsequent plasma levels of Paracetamol; however, there is no evidence that syrup of ipecac administered later than 60 minutes post ingestion is useful.

Administration of antidote to Paracetamol
Immediately administer acetylcysteine orally or with a nasogastric tube if 8 hours or more have elapsed from the reported time of ingestion of Paracetamol overdose.

The following procedures are recommended:

- Administer the oral loading dose of acetylcysteine, 140 mg/kg of body weight.
- Four hours after the loading dose, administer the first of 17 oral maintenance doses, 70 mg/kg of body weight. The oral maintenance dose is then repeated at 4-hour intervals for a total of 17 maintenance doses. If liver enzymes continue to be elevated, acetylcysteine may be continued beyond the full course of therapy until liver enzymes are decreasing and prothrombin time is returning to normal.

- If the patient vomits the loading dose or any maintenance dose within 1 hour of administration, repeat the dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonists of the μ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

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

Tramadol hydrochloride/Paracetamol is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

5.2 PHARMACODYNAMIC PROPERTIES

Effects on the Central Nervous System

Tramadol produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Tramadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Tramadol causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Tramadol produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension. The effect of oral tramadol on the QTcF interval was evaluated in a double-blind, randomized, four-way crossover, placebo- and positive- (moxifloxacin) controlled study in 68 adult male

and female healthy subjects. At a 600 mg/day dose (1.5-fold the maximum immediate-release daily dose), the study demonstrated no significant effect on the QTcF interval.

Effects on the Endocrine System
Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.
Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in invitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships
The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent opioid agonists. The minimum effective analgesic concentration of tramadol for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance

Concentration–Adverse Reaction Relationships
There is a relationship between increasing tramadol plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

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

After a single oral administration of a tramadol/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 µg/ml (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives t1/2 are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2,5 h (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Tramadol hydrochloride/Paracetamol, no clinical significant change

was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

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

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

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

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

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism:
Tramadol is extensively 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 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. NONCLINICAL PROPERTIES
6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
There are no animal or laboratory studies on the combination product (tramadol and Paracetamol) to evaluate carcinogenesis, mutagenesis, or impairment of fertility. Data on the individual components are described below.

Carcinogenesis
A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.5 times the maximum recommended daily human dosage or MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No
evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water (1 times the MRHD).
Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of Paracetamol. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing Paracetamol up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 1.2 times the maximum human daily dose (MHDD) of 2.6 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (1.1 times) or mice (1.9-2.2 times the MHDD, based on a bodysurface area comparison).

Mutagenesis
Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the in vitro bacterial reverse mutation assay using Salmonella and E. coli (Ames), the mouse lymphoma assay in the absence of metabolic activation, the in vitro chromosomal aberration assay, or the in vivo micronucleus assay in bone marrow. Paracetamol was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, Paracetamol tested positive for induction of sister chromatid exchanges and chromosomal aberrations in in vitro assays using Chinese hamster ovary cells. In the published literature, Paracetamol has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750

mg/kg/day (2.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of Fertility
No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. These dosages are 1.6 and 2.4 times the MRHD. In studies of Paracetamol conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of Paracetamol, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal
sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of Paracetamol near the upper limit of daily dosing.

Published studies in rodents report that oral Paracetamol treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

7. DESCRIPTION
Acuvin is supplied for oral administration, as film coated tablet of Paracetamol and Tramadol Hydrochloride. Each Film-Coated Tablet of Acuvin contains Paracetamol 325 mg and Tramadol Hydrochloride 37.5 mg.

8. PHARMACEUTICAL PARTICULARS
8.1 INCOMPATIBILITIES
Not Applicable

8.2 SHELF-LIFE
Refer pack

8.3 PACKAGING INFORMATION
Refer pack

8.4 STORAGE AND HANDING INSTRUCTIONS
Refer pack

9. PATIENT COUNSELLING INFORMATION
ACUVIN is:

• A strong prescription pain medicine that contains an opioid (narcotic) that is used for the short-term (five days or less) management of acute pain, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.
• An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about ACUVIN:
• Get emergency help right away if you take too much ACUVIN (overdose). When you first start taking ACUVIN, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
• ACUVIN can cause severe drowsiness, breathing problems (respiratory depression), coma and death when taken with benzodiazepines or other medicines that depress consciousness.
• Never give anyone else your ACUVIN. Store ACUVIN away from children and in a safe place to prevent stealing or abuse. Selling or giving away ACUVIN is against the law.
• Get emergency help right away if you take more than 4,000 mg of Paracetamol in 1 day. Taking ACUVIN with other products that contain Paracetamol can lead to serious liver problems and death.

Important Information Guiding Use in Pediatric Patients:
• Do not give ACUVIN to a child younger than 12 years of age.
• Do not give ACUVIN to a child younger than 18 years of age after surgery to remove the tonsils and/or adenoids.
• Avoid giving ACUVIN to children between 12 to 18 years of age who have risk factors for breathing problems such as obstructive sleep apnea, obesity, or underlying lung problems.

Do not take ACUVIN if you have:
• Severe asthma, trouble breathing, or other lung problems.
• A bowel blockage or have narrowing of the stomach or intestines.
• An allergy to any of its ingredients (e.g., tramadol hydrochloride or Paracetamol).
• Taken a Monoamine Oxidase Inhibitor, MAOI, (medicine used for depression) within the last 14 days.

Before taking ACUVIN, tell your healthcare provider if you have a history of:
• head injury, seizures
• liver, kidney, thyroid problems
• problems urinating
• pancreas or gallbladder problems
• abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
• pregnant or planning to become pregnant. Prolonged use of ACUVIN during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
• breastfeeding. Not recommended; it may harm your baby.

• taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking ACUVIN with certain other medicines can cause serious side effects that could lead to death.

When taking ACUVIN:
• Do not change your dose. Take ACUVIN exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
• Take your prescribed dose: 2 tablets every 4 to 6 hours as needed for pain relief for a maximum of 5 days. Do not take more than your prescribed dose and do not take more than 8 tablets per day.
Talk to your doctor before taking ACUVIN if you::
Suffer from depression and you are taking antidepressants as some of them may interact with tramadol.
Possible side effect: Serotonin syndrome, that can manifest as mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as fever, increase in heart rate, unstable blood pressure, involuntary twitching, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

If you miss a dose, take your next dose at your usual time.
• Call your healthcare provider if the dose you are taking does not control your pain.
• If you have been taking ACUVIN regularly, do not stop taking ACUVIN without talking to your healthcare provider.
• After you stop taking ACUVIN, ask your pharmacist how to dispose of any unused tablets.

While taking ACUVIN DO NOT:
• Drive or operate heavy machinery, until you know how ACUVIN affects you. ACUVIN can make you sleepy, dizzy, or lightheaded.
• Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ACUVIN may cause you to overdose and die.
The possible side effects of ACUVIN:
• constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:
• trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion

10. DETAILS OF MANUFACTURER
MANUFACTURED BY:
Refer pack for manufacturer details.

MARKETED BY:
Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4. Gala No. 1 to 3 & 11 to 13
Ground Floor, 101 to 106 & 111 to 116 First Floor,
201 to 206 & 211 to 216 2nd Floor, Pimplas,
Dist. Thane, Bhiwandi – 421302, India
TM-Trade Mark of Abbott Healthcare Pvt. Ltd.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
Refer pack for Permission/License details.

12. DATE OF REVISION
Version 7.0, dated 12th Feb 2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com