1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

TRAMADOL HYDROCHLORIDE AND ACETAMINOPHEN TABLETS USP

2. Qualitative and quantitative composition

SR. NO	NAME OF THE INGREDIENTS	PURPOSE	LABLE CLAIM	OVERAGES %	QTY. / TABLET	PHARMACOPEIAL SPECIFICATION
ACTIVE INGREDIENTS						
1.	Tramadol Hydrochloride	API	37.50 mg	0.00 %	37.500 mg	USP
2.	Acetaminophen	API	325.00 mg	0.00 %	325.000 mg	USP
INACTIVE INGREDIENTS						
3.	Maize Starch	Diluent	-	0.00 %	70.000 mg	BP
4.	Colloidal Silicon Dioxide	Glidant	-	0.00 %	2.000 mg	USP
5.	Microcrystalline Cellulose	Diluent	-	0.00 %	70.000 mg	BP
6.	Sodium Benzoate	Preservative	-	0.00 %	0.500 mg	BP
7.	Demineral Water	Vehicle	-	0.00 %	0.100 ml	INHOUSE
8.	Maize Starch	Binder	-	0.00 %	20.000 mg	BP
9.	Povidone	Binder	-	0.00 %	5.000 mg	BP
10.	Magnesium Stearate	Lubricant	-	0.00 %	4.000 mg	BP
11.	Purified Talc	Glidant	-	0.00 %	10.000 mg	BP
12.	Sodium Starch Glycolate	Disintegrant	-	0.00 %	4.000 mg	BP
13.	Colloidal Silicon Dioxide	Glidant	-	0.00 %	2.000 mg	USP
14.	Iron Oxide Yellow colour	Colour	-	0.00 %	0.200 mg	INHOUSE
15.	Acetone*	Solvent	-	0.00 %	0.080 ml	BP
16.	Isopropyl Alcohol*	Solvent	-	0.00 %	0.080 ml	BP
17.	Wesco Coating Material	Coating	-	0.00 %	4.800 mg	INHOUSE

*Evaporates during manufacturing, does not remain in final formulation.

3. Pharmaceutical form

Oral Tablet

4. Clinical particulars

4.1 Therapeutic indications

Tramadol Hydrochloride and Acetaminophen tablets are indicated for the symptomatic treatment of moderate to severe pain.
The use of Tramadol Hydrochloride and Acetaminophen tablets should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and acetaminophen.

4.2 Posology and method of administration

Posology:
Adults and adolescents (12 years and older)
The use of Tramadol Hydrochloride and Acetaminophen tablets should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and acetaminophen.
The dose should be individually adjusted according to intensity of pain and response of the patient.
An initial dose of two tablets of Tramadol Hydrochloride and Acetaminophen tablet is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 300 mg tramadol and 2600 mg acetaminophen) per day.
The dosing interval should not be less than six hours.
Tramadol Hydrochloride and Acetaminophen tablets should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with Tramadol Hydrochloride and Acetaminophen tablet 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.
Children
The effective and safe use of Tramadol Hydrochloride and Acetaminophen tablets has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.
Elderly patients
The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half life of tramadol was increased by 17% following oral administration. In patients over 75 years old, it is recommended that the minimum interval between doses should be not less than 6 hours, due to the presence of tramadol.
Renal insufficiency
Because of the presence of tramadol, the use of Tramadol Hydrochloride and Acetaminophen tablet is not recommended in patients with severe renal impairment (creatinine clearance < 10 ml/min). In cases of moderate renal impairment (creatinine clearance between 10 and 30 ml/min), the dosing should be increased to 12-hourly intervals. As tramadol is removed only very slowly by haemodialysis or by haemofiltration, post dialysis administration to maintain analgesia is not usually required.
Hepatic Insufficiency
In patients with severe hepatic impairment Tramadol Hydrochloride and Acetaminophen tablets should not be used. In moderate cases prolongation of the dosage interval should be carefully considered.

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 substances or to any of the excipients of the medicinal product.
- Acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs.
- Acetaminophen And Tramadol Hydrochloride tablets USP 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:
The maximum dose of 8 tablets of Tramadol Hydrochloride and Acetaminophen tablets should not be exceeded in adults and adolescents 12 years and older. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other acetaminophen (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.
In severe renal impairment (creatinine clearance <10 ml/mm), Tramadol Hydrochloride and Acetaminophen tablet is not recommended.
In patients with severe hepatic impairment Tramadol Hydrochloride and Acetaminophen tablets should not be used. The hazards of acetaminophen 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 impairment, Tramadol Hydrochloride and Acetaminophen tablet 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 Tramadol Hydrochloride and Acetaminophen tablets 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.
Precautions:
Tramadol Hydrochloride and Acetaminophen tablets should be used with caution in opioid dependent patients, or in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory centre or the respiratory function, or with an increased intracranial pressure.
Acetaminophen in overdosage may cause hepatic toxicity in some patients.
At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported.
Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur.

In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is contraindicated with:
Non-selective MAO Inhibitors: Risk of serotoninergic syndrome (diarrhoea, tachycardia, sweating, trembling, confusion, even coma).
Selective-A MAO Inhibitors: Extrapolation from non-selective MAO inhibitors, risk of serotoninergic syndrome (diarrhoea, tachycardia, sweating, trembling, confusion, even coma).
Selective-B MAO Inhibitors: Central excitation symptoms evocative of a serotoninergic syndrome (diarrhoea, tachycardia, sweating, trembling, confusion, 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: 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

- In isolated cases there have been reports of Serotonin Syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicines such as selective serotonin re-uptake inhibitors (SSRIs) and triptans. Signs of Serotonin Syndrome may be for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.
- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates: 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), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen. These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
- As medically appropriate, periodic evaluation of prothrombin time should be performed when Acetaminophen And Tramadol Hydrochloride tablets USP and warfarin like compounds are administered concurrently due to reports of increased INR.
- Other drugs known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.
- Medicinal products reducing the seizure threshold, such as bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and narcoleptics. Concomitant use of tramadol with these drugs can increase the risk of convulsions. The speed of absorption of Acetaminophen may be increased by metoclopramide or Domperidone and absorption reduced by Cholestyramine.
- In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Pregnancy and lactation

Pregnancy:
Since Tramadol Hydrochloride and Acetaminophen tablet is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.
Acetaminophen: Epidemiological studies in human pregnancy have shown no ill effects due to acetaminophen used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.
Tramadol: There are no adequate data from the use of tramadol in pregnant women. Tramadol crosses the placental barrier and chronic use during pregnancy can cause withdrawal symptoms in the new-born baby. Therefore, it should not be used during pregnancy.
Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in respiratory rate which are not usually clinically relevant.
Lactation:
Since Tramadol Hydrochloride and Acetaminophen tablet is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.
Acetaminophen: Acetaminophen is excreted in breast milk but not in a clinically significant amount. Available published data on acetaminophen does not contraindicate it for breast feeding.
Tramadol: Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest 0.1% of the dose given to the mother. Tramadol hydrochloride should not be administered during breast feeding.

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.

4.8 Undesirable effects

Undesirable effects that may occur during treatment with Acetaminophen and Tramadol Hydrochloride tablets USP are classified into the following groups in order of frequency:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The most commonly reported undesirable effects during the clinical trials performed with the acetaminophen/tramadol combination were nausea, dizziness and somnolence, observed in more than 10% of the patients.
Cardiac disorders: Uncommon: hypertension, palpitations, tachycardia, arrythmia.
Nervous system disorders: Very common: dizziness, somnolence, Common: headache trembling, Uncommon: involuntary muscular contractions, paraesthesia, tinnitus, Rare: ataxia, convulsions.
Psychiatric disorders:
Common: confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders, Uncommon: depression, hallucinations, nightmares, amnesia, Rare: drug dependence.
Post marketing surveillance: Very rare: abuse.
Eye disorders: Rare: blurred vision
Respiratory, thoracic and mediastinal disorders: Uncommon: dyspnoea

Gastro-intestinal disorders: Very common: nausea**,** Common: vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence**,** Uncommon: dysphagia, melaena.
Hepatobiliary disorders: Uncommon: hepatic transaminases increase.
Skin and subcutaneous tissue disorders: Common: sweating, pruritus, Uncommon: dermal reactions (e.g. rash, urticaria).
Renal and urinary disorders: Uncommon: albuminuria, micturition disorders (dysuria and urinary retention).
General disorders and administration site condition: Uncommon: shivers, hot flushes, thoracic pain.
Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or acetaminophen cannot be excluded:

Tramadol

- Postural hypotension, bradycardia, collapse (tramadol).
- Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
- Rare cases: allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
- Rare cases: changes in appetite, motor weakness, and respiratory depression.
- Psychic side-effects may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood, (usually elation occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behavior perception disorders).
- Worsening of asthma has been reported though a causal relationship has not been established.
- Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

Acetaminophen

- Adverse effects of acetaminophen are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to acetaminophen.
- There have been several reports that suggest that acetaminophen may produce hypoprothrombinaemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

4.9 Overdose

Tramadol Hydrochloride and Acetaminophen tablet is a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or acetaminophen 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, and

cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Symptoms of overdose from Acetaminophen:

An overdose is of particular concern in young children. Symptoms of acetaminophen 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 acetaminophen. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of acetaminophen 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 acetaminophen 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 Tramadol Hydrochloride and Acetaminophen tablets with haemodialysis or haemofiltration alone is not suitable for detoxification.
- Immediate treatment is essential in the management of acetaminophen 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 acetaminophen in the preceding 4 hours or any child who has ingested 150 mg/kg of acetaminophen in the preceding 4 hours should undergo gastric lavage. Acetaminophen 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 acetaminophen overdose nomogram). Administration of intravenous N-acetylcysteine (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 acetaminophen ingested, the antidote for acetaminophen, 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: Opioids in combination with non-opioid analgesics**, ATC code:** N02AJ13
Analgesics: Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is 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.
Mechanism of action
Tramadol is a centrally acting opioid analgesic which binds to mu-opioid receptors and weakly inhibits the reuptake of norepinephrine and serotonin. Acetaminophen, a Para-aminophenol derivative, has analgesic, antipyretic and weak anti-inflammatory activity. Used together, tramadol and acetaminophen combination has a faster onset of action compared to tramadol alone and longer duration of action compared to acetaminophen alone.

5.2 Pharmacokinetic properties

Absorption: Tramadol: Readily absorbed from GI tract; mean absolute bioavailability 75-90%. Acetaminophen: Readily absorbed from GI tract, peak plasma concentrations reached in 10-60 minutes.
Distribution: Tramadol: Widely distributed, crosses the placenta and distributes into the breast milk; protein binding: 20%. Acetaminophen: Widely distributed; crosses placenta and distributes into breast milk; negligible protein binding.
Metabolism: Tramadol: Undergoes metabolism by the cytochrome P450 isoenzymes CYP3A4 and CYP2D6; one of the metabolites, O-desmethyltramadol is pharmacologically active. Acetaminophen: Metabolised in liver.
Excretion: Tramadol: Excreted via urine as metabolites (60%) and unchanged drug (30%); elimination half-life of O-desmethyltramadol: 7 hr. Acetaminophen: Excreted mainly in urine as metabolites and unchanged drugs (<5%); elimination half-life: 1-3 hr.

5.3 Preclinical safety data

No preclinical study has been performed with the fixed combination (tramadol and acetaminophen) 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/acetaminophen.
The combination tramadol/acetaminophen has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/acetaminophen), 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/acetaminophen) 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. No effect on fertility has

been observed after oral administration of tramadol up to doses of 50 mg/kg in the male rat and 75 mg/kg in the female rat.
Extensive investigations showed no evidence of a relevant genotoxic risk of acetaminophen at therapeutic (i.e. non-toxic) doses.
Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of acetaminophen.
Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

6. Pharmaceutical particulars

6.1 List of excipients

- Maize Starch
- Colloidal Silicon Dioxide
- Microcrystalline Cellulose
- Sodium Benzoate
- Demineral Water
- Povidone
- Magnesium Stearate
- Purified Talc
- Sodium Starch Glycolate
- Iron Oxide Yellow colour
- Acetone
- Isopropyl Alcohol
- Wesco Coating Material

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Store in a dry place at a temperature below 30°c.

6.5 Nature and contents of container

2 x 10 Tablets Alu-Alu Pack, Packed in Printed and Laminated Carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

West Coast Pharmaceutical Works LTD, Ahmedabad

8. Marketing authorisation number(s)

Not applicable

9. Date of first authorisation/renewal of the authorisation

Not applicable

10. Date of revision of the text

December, 2017