SUMMARY OF PRODUCT CHARACTERISTICS

1. **Name of the Medicinal Product: Brand Name**:
   TRAMACETAL TABLETS (Acetaminophen and Tramadol Hydrochloride Tablets USP)

2. **Qualitative and Quantitative composition**

Each film coated tablet contains:

Acetaminophen USP.....325 mg

Tramadol Hydrochloride USP.....37.5 mg

Excipients.....q.s.

3. **Pharmaceutical Form**

Solid Dosage form

(Film coated tablet).

Description : Yellow coloured oblong film coated tablets with bisecting line on one side. 4. Clinical particulars

4.**1 Therapeutic Indications**

Tramacetal is a centrally acting synthetic analgesi.

4.2 Posology and Method of Administration:

For the short-term (five days or less) management of acute pain, the recommended dose of Tramacetal is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. Method of administration Oral Tablets.

4.3 Contraindications

Tramacetal is contra-indicated in patients with a known hypersensitivity to tramadol, Acetaminophen or other opioids such as codeine. It is also contraindicated in cases of severe liver function impairment and in acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic medicines. It should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal. Tramacetal must not be used for narcotic withdrawal treatment. Tramacetal should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions. Tramacetal should not be given to patients with respiratory depression especially in the presence of cyanosis and excessive bronchial secretions. Tramacetal should not be given to patients with increased intracranial

pressure or central nervous system depression due to head injury or cerebral disease.

4.4 Special Warnings and Precautions

Use Dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should take Acetaminophen containing products under medical supervision. Tramacetal may only be taken with special care in opioid dependence, reduced level of consciousness of uncertain origin, disorders of the respiratory function and increased intracranial pressure. Seizures: Seizures have been reported in patients receiving tramacetal at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients taking tricyclic anti-depressants or other tricyclic compounds e.g. promethazine, selective serotonin re-uptake inhibitors, MAO-inhibitors and neuroleptics. The risk of seizures may also be increased in patients with epilepsy, with a history of seizures or in patients with a recognized risk for seizures e.g. drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramacetal overdose. Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with tramacetal.

4.5 Interaction with other medicinal products and other forms of interaction:

Concomitant administration of Tramaccetal and Carbamazepine may cause significantly decreased tramadol and M1 concentrations. Patients receiving carbamazepine may have significantly reduced analgesic effect from the tramadol component of Tramacetal. Concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, quinidine and amitriptyline could result in some inhibition of the metabolism of tramadol.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentration of tramadol. Therefore no alteration of the Tramacetal dosage regimen is recommended for patients receiving chronic cimetidine therapy. Tramacetal must not be combined with a MAO-inhibitor, or within 14 days of discontinuation of it, as potentiation of serotonergic and noradrenergic effects may result. Post- marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and rare alterations of warfarin effect including elevation of prothrombin times. Periodic evaluation of prothrombin time should be performed when Tramacetal is administered concurrently with warfarin like compounds. Concomitant administration of diflunisal and Acetaminophen produces a 50% increase in Acetaminophen plasma levels in normal volunteers.

Tramacetal should be used cautiously and patients should be monitored carefully.

4.6 Pregnancy and Lactation Use in pregnancy & lactation:

Safety during pregnancy and lactation has not been established. Tramacetal has been shown to cross the placenta. Use in Children: To be used in children over 16 years of age.

4.7 Effects on Ability to Drive and Use Machine

Tramacetal may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

4.8 Undesirable effects

The most frequently reported side effects were of the gastrointestinal and central nervous systems. Gastrointestinal System: Nausea, abdominal pain, constipation, flatulenece, vomiting; dry mouth; dyspepsia and diarrhoea. Central Nervous System and Psychiatric: Dizziness, headache, nervousness, anxiety, agitation, euphoria, emotional lability, hallucinations, hypertonia and tremor. Somnolence, insomnia, anorexia , anxiety, confusion, euphoria nervousness. Other reported side-effects include pruritus, fatigue, upper respiratory tract infection, increased sweating, hot flushes, rashes, and asthenia. Other side-effects reported with the use of tramacetal include anaphylaxis, increased liver enzyme values, postural hypotension or cardiovascular collapse and the potential for toxic Epidermal Necrolysis and Stevens-Johnson Syndrome.

Acetaminophen may cause allergic reactions and skin rash. The rash usually appears as red areas or allergic wheals and may be accompanied by fever and involvement of the mucous membranes. The use of Acetaminophen has been associated with the occurrence of neutropenia, pancytopenia, and leucopenia. Special Precautions: Do not co-administer Tramacetal with other tramadol or Acetaminophen containing products. Tramacetal should not be taken with alcohol containing beverages. The administration of Tramacetal concurrently with central nervous system (CNS) depressants such as alcohol, opioids, anaesthetic agents, phenothiazines, tranquilizers or sedative hypnotics is likely to intensity and prolong CNS effects. Tramacetal should be used with caution in patients with impaired renal function and in patients prone to convulsive disorders or in shock.

4.9 Overdose

The clinical presentation of overdosage may include the signs and symptoms of tramadol toxicity. Acetaminophen toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and or seizures. Primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all symptoms caused by overdosage, the risk of seizures is also increased with naloxone administration. Treatment of restlessness and or convulsion is symptomatic and supportive. Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with Tramacetal with haemodialysis or haemofiltration alone is therefore not suitable for detoxification. 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. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias have been reported. Symptoms during the first 2 days of acute poisoning do not reflect the potential seriousness of the overdosage. Nausea, vomiting, anorexia and abdominal pain may persist for a week or more. Liver injury may become manifest on the second day, (or later) initially by elevation of serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of prothrombin time. The liver damage may progress to encephalopathy, coma and death. Cerebral oedema and non-specific myocardial depression have also occurred. In the event of overdosage consult a doctor or take the patient to the nearest hospital immediately. Specialised treatment is essential as soon as possible. Prompt treatment is essential. Any patient who has ingested about 7,5 g of Acetaminophen in the preceding 4 hours should undergo gastric lavage. Specific therapy with an antidote such as acetylcysteine or methionine may be necessary. If decided upon, acetylcysteine should be administered intravenously as soon as possible.

Acetylcysteine: Acetylcysteine should be administered as soon as possible. Preferably within 8 hours of overdosage.

ntravenously: An initial dose of 150 mg/ kg in 200 ml glucose injection, given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 ml of glucose injection over the next 4 hours, and then 100 mg/kg in 1000 ml over the next 16 hours. The volume of intravenous fluids should be modified for children. Orally : 140 mg/Kg as a 5% solution initially, followed by 70 mg/kg solution every 4 hours for 17 doses. Acetylcysteine is effective if administered within 8 hours of overdosage.

5. Pharmacological Particulars

5.1 Pharmacodynamic Properties

Pharmacological action:

Tramacetal is a centrally actine synthetic analgesic. Acetaminophen also has centrally acting analgesic effects. Pharmacodynamics: Tramacetal contains tramadol and Acetaminophen. Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ- opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the 0-demethylated metabolite M1 to μ-Opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-Opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound. Acetaminophen is a non-opiate, non-salicylate analgesic. Pharmacokinetics: Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Tramadol has a slower absorption and longer half-life when compared to Acetaminophen.

Absorption : The absolute bioavailability of tramadol from Tramacetal Tablets has not been determined. Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of Tramacetal tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two Tramacetal tablets occurs at approximately two and three hours, respectively, post-dose. Peak plasma concentrations of Acetaminophen occur within one hour and are not affected by coadministration with tramadol. Oral absorption of Acetaminophen following administration of Tramacetal occurs primarily in the small intestine.

Food effects: When Tramacetal was administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for Acetaminophen. However, peak plasma concentrations, and the extents of absorption, of tramadol and Acetaminophen were not affected. The clinical significance of this difference is unknown. Distribution: The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration upto 10 μg/mL. Saturation of plasma protein binding occurs

only at concentrations outside the clinically relevant range. Acetaminophen 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 Acetaminophen is bound to plasma protein. Metabolism : Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be N-and O- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (O-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response. Elimination : Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of Tramacetal. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of Tramacetal. The half-life of Acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of Acetaminophen is excreted unchanged in the urine.

6. Pharmaceutical Particulars

6.1 List of Excipients

Raw Material

Dibasic calcium phosphate

Anhydrous Microcrystalline cellulose

Starch Sodium

starch Glycolate

Magnesium stearate

Talcum Powder Opadry II (85G82932)

Yellow Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf Life:

24 Months

6.4 Special Precautions for Storage:

Store in a dry place, below 30º C. Protect from light. Keep out of reach of children

6.5 Nature and Contents of Container:

Alu–PVC Blister pack of 1 x 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. **Marketing Authorisation Holder And Manufacturing Site Addresses**

Marketing Authorisation Holder:

Cachet Pharmaceuticals Private Limited 415, Shah Nahar Industrial Estate, Dr. E. Moses Road, Worli, Mumbai-400 018, Maharashtra, India.
Manufacturer's Name and Address: Cachet Pharmaceuticals PVT. LTD. Village Thana, Baddi, Dist. Solan, Himachal Pradesh-Pin – 173 205, India.

8.Marketing Authorization Numbers

H2011/21776/193

9. Date of First Authorization/ Renewal of the Authorization

30/06/2011

10. Date of Revision of the Text

17.06.2026