SUMMARY OF PRODUCT CHARACTERISTICS:

1. Name of the medicinal product

TRAMACETAL TABLETS (Acetaminophen and Tramadol Hydrochloride Tablets)

2. Qualitative and quantitative composition

Batch Formula

Composition:

Each film coated tablet contains:

Acetaminophen USP……325 mg

Tramadol Hydrochloride USP……37.5 mg

Excipients…….q.s.

3. Pharmaceutical form

Film-coated tablet

4. Clinical particulars

4.1 Therapeutic indications

Acetaminophen and Tramadol Hydrochloride Tablets are indicated for the symptomatic treatment of moderate to severe pain.

The use of Acetaminophen and Tramadol Hydrochloride 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 Acetaminophen and Tramadol Hydrochloride 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 Acetaminophen and Tramadol Hydrochloride Tablets 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.

Acetaminophen and Tramadol Hydrochloride Tablets should under no circumstances be administered for longer than is strictly necessary (see also section 4.4 - Special warnings and precautions for use). If repeated use or long term treatment with Acetaminophen and Tramadol Hydrochloride Tablets 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 Acetaminophen and Tramadol Hydrochloride 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 Acetaminophen and Tramadol Hydrochloride Tablets is not recommended in patients with severe renal insufficiency (creatinine clearance < 10 ml/min). In cases of moderate renal insufficiency (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 Acetaminophen and Tramadol Hydrochloride 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 tramadol, Acetaminophen 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 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 Acetaminophen and Tramadol Hydrochloride Tablets 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 Acetaminophen (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.
- In severe renal insufficiency (creatinine clearance <10 ml/mm), Acetaminophen and Tramadol Hydrochloride Tablets is not recommended.
- In patients with severe hepatic impairment Acetaminophen and Tramadol Hydrochloride 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 insufficiency, Acetaminophen and Tramadol Hydrochloride Tablets 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 Acetaminophen and Tramadol Hydrochloride 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 for use

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. Acetaminophen and Tramadol Hydrochloride Tablets 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.

Acetaminophen 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 tapering it at the time of discontinuation especially after long treatment periods. 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.

Acetaminophen and Tramadol Hydrochloride 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.

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

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 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 neuroleptics. 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 Acetaminophen and Tramadol Hydrochloride Tablets is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

• Data regarding Acetaminophen:

Epidemiological studies in human pregnancy have shown no ill effects due to Acetaminophen 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.

Lactation:

Since Acetaminophen and Tramadol Hydrochloride Tablets is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

• Data regarding Acetaminophen:

Acetaminophen 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 Acetaminophen.

• Data regarding tramadol:

Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol should not be ingested 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.

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

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.

Cardiovascular system disorders:

• Uncommon (≥ 1/1000 to < 1/100): hypertension, palpitations, tachycardia, arrythmia.

Central and peripheral nervous system disorders:

• Very common (≥ 1/10): dizziness, somnolence

• Common (≥ 1/100 to < 1/10): headache trembling

• Uncommon (≥ 1/1000 to < 1/100): involuntary muscular contractions, paraesthesia, tinnitus

• Rare (≥ 1/10000 to < 1/1000): ataxia, convulsions, syncope.

Psychiatric disorders:

• Common (≥ 1/100 to < 1/10): confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders

• Uncommon (≥ 1/1000 to < 1/100) : depression, hallucinations, nightmares, amnesia

• Rare (≥ 1/10000 to < 1/1000): drug dependence.

Post marketing surveillance

very rare (< 1/10000): abuse.

Vision disorders:

• Rare (≥ 1/10000 to < 1/1000): blurred vision

Respiratory system disorders:

• Uncommon (≥ 1/1000 to < 1/100): dyspnoea

Gastro-intestinal disorders:

• Very common (≥ 1/10) : nausea

• Common (≥ 1/100 to < 1/10): vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence

• Uncommon (≥ 1/1000 to < 1/100): dysphagia, melaena.

Liver and biliary system disorders:

• Uncommon (≥ 1/1000 to < 1/100): hepatic transaminases increase.

Skin and appendages disorders:

• Common (≥ 1/100 to < 1/10) : sweating, pruritus

• Uncommon (≥ 1/1000 to < 1/100): dermal reactions (e.g.rash, urticaria).

Urinary system disorders:

• Uncommon (≥ 1/1000 to < 1/100): albuminuria, micturition disorders (dysuria and urinary retention).

Body as a whole:

• Uncommon (≥ 1/1000 to < 1/100): shivers, hot flushes, thoracic pain.

Metabolism and nutrition disorders:

• Unknown: hypoglycaemia

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 (≥ 1/10000 to < 1/1000) : allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

• Rare cases (≥ 1/10000 to < 1/1000) : 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 behaviour 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 hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

4.9 Overdose

Acetaminophen and Tramadol Hydrochloride Tablets 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, 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 Acetaminophen and Tramadol Hydrochloride 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 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 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: Analgesics combinations,

ATC code: N02AX52

Analgesics

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 Acetaminophen is unknown and may involve central and peripheral effects.

Acetaminophen and Tramadol Hydrochloride Tablets is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

5.2 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 Acetaminophen.

After a single oral administration of a tramadol/Acetaminophen (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 µg/ml (Acetaminophen) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (Acetaminophen) respectively. The mean elimination half-lives $t_{1/2}$ are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2,5 h (Acetaminophen).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Tramadol Hydrochloride and Acetaminophen Tablets, 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 and Acetaminophen Tablets, the oral absorption of Acetaminophen is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of Acetaminophen are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration of Acetaminophen and Tramadol Hydrochloride Tablets with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or Acetaminophen so that Acetaminophen and Tramadol Hydrochloride Tablets 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%.

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 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.

Acetaminophen 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 Acetaminophen is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Acetaminophen is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9 % of Acetaminophen is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

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

Dibasic calcium phosphate
Microcrystalline cellulose
Maize starch
Maize starch (for paste)
Sodium starch Glycolate
Magnesium stearate
Purified talc
Opadry yellow (85G82932)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a dry place, below 30^{o}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

Not Applicable

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Cachet Pharmaceuticals Private Limited

Address: 415, Shah Nahar Ind. Estate,

Dr. E. Moses Road, Worli,

Mumbai-400 018

Maharashtra, India

Telephone: +91-22-24970011 / +91-22-40829999

8. MARKETING AUTHORISATION NUMBER

-Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

-Not applicable

10. DATE OF REVISION OF THE TEXT

-Not applicable

11. NAME AND ADDRESS OF MANUFACTURE

Cachet Pharmaceuticals Private Limited

Address: Village: Thana, Baddi, Himachal Pradesh-173 205, India