Summary of Product Characteristics

1. Name of Medicinal Product

ACECLOFENAC, PARACETAMOL & TRAMADOL TABLETS

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Composition of the Drug product:

Each film coated tablet Contains:

Aceclofenac BP 100mg

Paracetamol BP 325 mg

Tramadol Hydrochloride BP 37.5 mg Excipients q.s.

Colour: Sunset yellow FCF & Titanium Dioxide

Quantitative composition and function of each ingredients is listed

Batch Size: 1,00,000 Tablets

Manufacturing Formula			**Requirement as per batch size**			
Sr. No.	**Name of Ingredients**	**Spec.**	**Label claim / tab in mg**	**% Overage**	**Qty per tablet**	**Std. Qty per batch in Kg.**
CORE TABLET FORMULA						
01	Aceclofenac	BP	100.00	0%	100.00	10.00 kg
02	Paracetamol	BP	325.00	0%	325.00	32.50 kg
03	Tramadol HCL	BP	37.5	0%	37.5	3.75 kg
04	Starch (dried)	BP			51.0	5.10 kg
05	Dibasic Calcium phosphate	BP			70.85	7.085 kg
06	Starch (for Paste) (dried)	BP			30.000	3.00 kg
07	Povidone (PVP K-30)	USP			5.500	0.55 kg
08	Sorbitol 70% solution	USP			5.500	0.55 kg
09	Talc	BP			2.750	0.275 kg
10	Magnesium Stearate	BP			1.650	0.165 kg
11	Starch (dried)	BP			2.750	0.275 kg
COATING						
01	Sunset yellow	BP			7.00	0.70 kg
02	Titanium Dioxide	BP			12.00	1.20 kg
03	Iso propyl alcohol	BP	QS		0.25 ml	0.025 lit
04	Methylene chloride	BP	QS		0.13 ml	0.013 lit

3. Pharmaceutical Form

Tablets

A Yellow coloured, Capsule shaped, Biconvex, film coated tablets having Breakline on one side.

4. Clinical Particulars

4.1. Therapeutic indications:

It Is Prescribed For Fever, Various Kinds Of Pain And Arthritis.

Aceclofenac/Tramadol hydrochloride/Paracetamol tablets are indicated for the symptomatic treatment of moderate to severe pain.

The use of Aceclofenac/Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of Aceclofenac, tramadol and paracetamol.

4.2. Posology and method of administration:

Posology

Adults and adolescents (12 years and older)

The use of Aceclofenac/Tramadol hydrochloride/Paracetamol should be restricted to patients whose moderate to severe pain is considered to require a combination of Aceclofenac, tramadol and paracetamol.

The dose should be individually adjusted according to intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

An initial dose of two tablets of Aceclofenac/Tramadol hydrochloride/Paracetamol is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (equivalent to 800 mg Aceclofenac, 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Aceclofenac/Tramadol hydrochloride/Paracetamol should under no circumstances be administered for longer than is strictly necessary. If repeated use or long term treatment with

Aceclofenac/Tramadol hydrochloride/Paracetamol is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Paediatric population

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

Elderly patients

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

Renal insufficiency/dialysis

Because of the presence of tramadol, the use of Aceclofenac/Tramadol hydrochloride/Paracetamol 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 impairment

In patients with hepatic impairment the elimination of tramadol is delayed. In these patients prolongation of dosage intervals should be carefully considered according to the patient's requirements.

Because of the presence of paracetamol should not be used in patients with severe hepatic impairment.

Method of administration

Oral use.

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

4.3. Contra-indications:

Hypersensitivity. Moderate to severe renal or hepatic impairment; severe heart failure; pregnancy (third trimester).

4.4. Special warning and precautions for use: -

GI disease; renal or hepatic impairment; alcohol-dependent patients; asthma or allergic disorders; haemorrhagic disorders; hypertension; cardiac impairment. Elderly. Caution when driving or operating machinery. Monitor renal and hepatic function and blood counts during long term treatment. Persistently elevated hepatic enzyme levels may require drug withdrawal. Pregnancy, lactation.

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

Paracetamol: Reduced Absorption Of Cholestyramine Within 1 Hr Of Administration. Accelerated Absorption With Metoclopramide. Aceclofenac: M0ay Increase The Plasma Concentrations Of Lithium And Digoxin. Increased Nephrotoxicity With Diuretics. Serum-Potassium Should Be Monitored When Used With Potassium-Sparing Diuretics. May Enhance Activity Of Anticoagulants. May Increase Plasma Methotrexate Levels Leading To Toxicity If Administered Within 2-4 Hr Of Methotrexate Admin. Risk Of Convulsions With Quinolones. Potentially Fatal: Paracetamol: Increased Risk Of Liver Damage In Chronic Alcoholics. Increased Risk Of Toxicity With High Doses Or Long Term Admin Of Barbiturates, Carbamazepine, Hydantoins, Isoniazid, Rifampin And Sulfinpyrazone.

4.6. Use in pregnancy and lactation:

Pregnancy

Since Aceclofenac/Tramadol hydrochloride/Paracetamol 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 dosage.

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 Aceclofenac/Tramadol hydrochloride/Paracetamol is a fixed combination of active ingredients including tramadol, it should not be used more than once during breast feeding or alternatively, breast-feeding should be discontinued during treatment with tramadol.

Data regarding paracetamol:

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data on paracetamol does not contraindicate it for 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.

Fertility

Post marketing surveillance does not suggest an effect of tramadol on fertility.

Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol.

4.7. Effects on ability to drive and operate machine:

Tramadol hydrochloride 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:

Paracetamol: nausea, allergic reactions, skin rashes, acute renal tubular necrosis.
Aceclofenac: diarrhoea, headache, vertigo, dizzies, nervousness, tinnitus, depression, drowsiness, insomnia; fever, angioedema, bronchospasm, rashes; blood dyscrasias. Potentially fatal: paracetamol: very rare, blood dyscrasias (eg, thrombocytopaenia, leucopaenia, neutropaenia, agranulocytosis); liver damage. Aceclofenac: severe gi bleeding; nephrotoxicity.
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 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.

Paracetamol

- Adverse effects of paracetamol 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 paracetamol.

- There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

- Very rare cases of serious skin reactions have been reported.

4.9. Overdose:

Aceclofenac/Tramadol hydrochloride/Paracetamol is a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

<u>Symptoms of overdose from tramadol</u>

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 paracetamol

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalophathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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

Emergency treatment

- Transfer immediately to a specialised unit.

- Maintain respiratory and circulatory functions.

- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.

- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.

- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.

- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.

- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramadol hydrochloride/Paracetamol with haemodialysis or haemofiltration alone is not suitable for detoxification.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested ≥150 mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous 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 paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.

5. Pharmacological Properties

5.1. Pharmaco-dynamic properties:

Pharmacotherapeutic group: other opioids, tramadol, combinations.

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

Aceclofenac is a phenylacetic acid derivative that inhibits synthesis of the inflammatory cytokines interleukin-1b and tumour necrosis factor, and inhibits prostaglandin e2 production. It increases glycosaminoglycans (gag) synthesis, the principal macromolecule of the extracellular matrix, which aids in repair and regeneration of articular cartilage. Thus, aceclofenac has +ve effects on cartilage anabolism combined with modulating effect of matrix catabolism. Paracetamol has analgesic and antipyretic action with weak anti-inflammatory activity. It produces analgesia by increasing pain threshold and antipyresis by acting on the hypothalamic heat-regulating centre. Absorption: aceclofenac: rapidly absorbed; almost 100% bioavailability; peak plasma levels reached about 1.25-3 hr after oral admin. Distribution: aceclofenac: >99.7% bound to plasma proteins; distributes into synovial fluid. Paracetamol: distributes throughout most fluids of the body. Metabolism: aceclofenac: probably metabolised by cyp2c9; average plasma elimination half-life: 4-4.3 hr. Paracetamol: mainly metabolised hepatically; plasma elimination half-life: 1-4 hr. Excretion: aceclofenac: about two-thirds of the administered dose is removed in the urine, mainly as conjugated hydroxymetabolites. Paracetamol: most metabolites are removed in the urine within 24 hr.

5.2. Pharmaco-kinetic 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 $t_{1/2}$ 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.

Biotransformation

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

Tramadol is metabolised through O-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through N-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect are 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 P450 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.

5.3. Pre-clinical safety data

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

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

The combination tramadol/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/paracetamol), i.e., 8.3 times the maximum

therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect 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 paracetamol 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 paracetamol.

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

6. Pharmaceutical Particulars

6.1 List of Excipients:

Maize Starch	BP
Dibasic calcium phosphate	BP
Starch paste	BP
Povidone (PVP K-30)	BP
Sorbitol 70% solution	BP
Talc	BP
Magnesium Stearate	BP
Sunset yellow FCF	BP

Titanium Dioxide	BP
Isopropyl Alcohol	BP
Methylene chloride	BP

6.2 Incompatibilities: Not Applicable

6.3 Shelf-life: 24 Months

6.4 Special precautions for storage: Store below 30ºC. Protect from light.

6.5 Nature and contents of container:

One Blister Pack of 10 Tablets and such one blister pack in monocarton with package insert and such 10 monocarton contain 1 outer carton.

6.6 Special precautions for disposal and other handling

No special requirements