SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

CEFLONAC FORTE

ACECLOFENAC 100 MG AND PARACETAMOL 500 MG TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each film coated tablet contains:
- Aceclofenac BP (100 mg)
- Paracetamol BP (500 mg)
- Approved colour used (-)
- -- (-- QS)

Sr. No.	Ingredients	Specification	Qty. (mg /Tab.)	Ovg. (%)
1.	Paracetamol	BP	500.000	--
2.	Aceclofenac	BP	100.000	--
3.	Maize Starch	BP	35.000	--
4.	Microcrystalline Cellulose (Avicel pH 101)	BP	25.000	--
5.	Sodium Starch Glycolate	BP	10.000	--
6.	Croscarmellose Sodium	BP	15.000	--
7.	Povidone (K – 30)	BP	5.000	
8.	Maize Starch (For Paste)	BP	20.000	
9.	*Purified Water	IH	q.s	
LUBRICATION				
10.	Colloidal Anhydrous Silica	BP	4.000	--
11.	Purified Talc	BP	6.000	
12.	Sodium Starch Glycolate	BP	10.000	
13.	Croscarmellose Sodium	BP	15.000	
14.	Magnesium Stearate	BP	5.000	--
15.	*Additional Maize Starch	BP	3.500	--
TOTAL			**750.000**	--
FILM COATING				

16.	HPMC E-15	BP	12.000	--	
17.	Purified Talc	BP	1.000	--	
18.	Propylene Glycol	BP	1.000	--	
19.	Colour Sunset Yellow Lake	IH	4.000	--	
20.	**Isopropyl Alcohol	BP	125.000	--	
21.	**Dichloromethane	BP	250.000	--	
TOTAL			**768.000**	--	

IHS: In House Specification

Average weight of uncoated tablets **:** 750.000 mg ± 5%
Average weight of coated tablets **:** 768.000 mg ± 5 %

*Includes additional Maize Starch to compensate loss on drying.

****** Isopropyl Alcohol and Dichloromethane is used as solvents so does not appear in the final product.

3. PHARMACEUTICAL FORM

Film coated tablet

4.CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Aceclofenac

Aceclofenac tablets are indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Paracetamol

Paracetamol has analgesic and antipyretic actions similar to those of aspirin and hence is a suitable alternative for patients sensitive to aspirin.

For the relief of mild to moderate pain and febrile conditions, *eg* headache, toothache, colds, influenza, rheumatic pain and dysmenorrhoea.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Aceclofenac

Aceclofenac tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid.

To be taken preferably with or after food. When Aceclofenac was administered to fasting and fed healthy volunteers only the rate and not the extent of aceclofenac absorption was affected.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

Adults

The recommended dose is 200 mg daily, taken as two separate 100 mg doses, one tablet in the morning and one in the evening.

Paediatric population

There are no clinical data on the use of Aceclofenac in children and therefore it is not recommended for use in children under 18 years of age.

Elderly

The elderly, who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication, are at increased risk of serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

The pharmacokinetics of Aceclofenac are not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency.

Renal insufficiency

There is no evidence that the dosage of Aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised.

Hepatic insufficiency

There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used.

Paracetamol

Posology

Adults including elderly and children over 12 years: One to two tablets every 4-6 hours as required, to a maximum of 8 tablets daily in divided doses.

Children 6-12 years: Half to one tablet every 4-6 hours as necessary, to a maximum of 4 tablets

daily in divided doses.

Children under 6 years: Not recommended for children under 6 years of age. Alternative presentations of paracetamol are recommended for paediatric usage in order to obtain suitable doses of less than 250mg.

Method of administration

Oral administration. Swallow the tablet whole with a glass of water. Do not crush or chew the tablets.

4.3 CONTRAINDICATIONS

Aceclofenac

Hypersensitivity to Aceclofenac or to any of the excipients.

Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of active bleedings or bleeding disorders

NSAIDS are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. Asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

Patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.Severe heart failure, hepatic failure and renal failure.

History of gastrointestinal bleeding or perforation, related to previous NSAIDS therapy.

Aceclofenac should not be prescribed during pregnancy, especially during the last trimester of pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

Paracetamol

Known hypersensitivity to paracetamol or other constituents in the tablets.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Aceclofenac

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

The use of Aceclofenac with concomitant NSAIDs including cyclooxygenase- 2 selective inhibitors should be avoided.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory disorders:

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients.

Renal:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, liver dysfunction, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Aceclofenac Tablets.

Patients with mild to moderate renal impairment should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly. Effects on renal function are usually reversible on withdrawal of Aceclofenac.

Hepatic:

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Aceclofenac Tablets should be

discontinued. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms.
Use of NSAIDs in patients with hepatic porphyria may trigger an attack.

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. As the cardiovascular risks of aceclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re- evaluated periodically.
Aceclofenac should also be administered with caution and under close medical surveillance to patients with congestive heart failure, significant risk factors for cardiovascular events and history of cerebrovascular bleeding.
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for aceclofenac.
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with aceclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.
Close medical surveillance is imperative in patients with:

• symptoms indicative of gastro-intestinal disorders involving either the upper or lower gastrointestinal tract
• with a history suggestive of gastro-intestinal ulceration, bleeding or perforation
• with ulcerative colitis or with Crohn's disease
• bleeding diathesis or haematological abnormalities.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients

with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin.

When GI bleeding or ulceration occurs in patients receiving aceclofenac, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Dermatological:

Impaired female fertility:

The use of Aceclofenac Tablets may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Aceclofenac Tablets should be considered.

Hypersensitivity/Dermatological reactions:

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Jonson syndrome, and toxic epidermal necrolysis, have been reporting very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can trigger serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out.

Thus, it is advisable to avoid use of Aceclofenac in case of varicella.

Haematological:

Aceclofenac Tablets may reversibly inhibit platelet aggregation (see anticoagulants under 'Interactions').

Long-term treatment:

All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal failure, hepatic function (elevation of liver enzymes may occur) and blood counts.

Paracetamol

Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

Care is advised in the administration of paracetamol to patients with alcohol dependency, severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND PHARMACEUTICAL FORM

Aceclofenac

Other analgesics including cyclooxygenase-2 selective inhibitors:

Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

Anti-hypertensives:

NSAIDs may reduce the effect of anti-hypertensives. The risk of acute renal insufficient, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ACE- inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Diuretics:

Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored.

Cardiac glycosides:

NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels.

Lithium and digoxin:

Several NSAID drugs inhibit the renal clearance of lithium, resulting in increased serum concentrations of both. The combination should be avoided unless frequent monitoring of lithium and digoxin levels can be performed.

Methotrexate:

Decreased elimination of methotrexate. The possible interaction between NSAIDs and methotrexate should be born in mind also when low doses of methotrexate are used, especially in patients with decreased renal function. When combination therapy has to be used, the renal function should be monitored. Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

Mifepristone:

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids:

Increased risk of gastrointestinal ulceration or bleeding.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin. Close monitoring of patients on combined anti-coagulants and Aceclofenac Tablets therapy should be undertaken.

Quinolone antibiotics:

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding

Cisclosporin, Tacrolimus:

Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus due to decreased synthesis of prostacyclin in the kidney. During combination therapy it is therefore important to carefully monitor renal function.

Zidovudine:

Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Antidiabetic agents:

Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects. Thus with Aceclofenac Tablets, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Other NSAIDs:

Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

Paracetamol

• Anticoagulants - the effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

• Metoclopramide – may increase speed of absorption of paracetamol.

• Domperidone – may increase speed of absorption of paracetamol.

• Colestyramine – may reduce absorption if given within one hour of paracetamol.

• Imatinib - restriction or avoidance of concomitant regular paracetamol use should be taken with imatinib.

4.6 PREGNANCY AND LACTATION

Aceclofenac

Pregnancy:

There is no information on the use of Aceclofenac during pregnancy. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development.

Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation or gastroschisis after use of prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Aceclofenac should not be given unless clearly necessary. If Aceclofenac is used by a women attempting to conceive, or during the first the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus) and on the possible risk of persistent pulmonary hypertension of the new born, use in the last trimester of pregnancy is contraindicated. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very

low doses.

- Inhibition of uterine contractions resulting in delayed or prolonged labour with an increased bleeding tendency in both mother and child.

Consequently, aceclofenac is contraindicated during the third trimester of pregnancy.

Lactation:

There is no information on the secretion of Aceclofenac to breast milk, there was however no notable transfer of radio labelled (14C) Aceclofenac to the milk of lactating rats.

The use of Aceclofenac Tablets should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

Fertility:

NSAIDs may impair fertility and are not recommended in women trying to conceive. The temporary discontinuation of Aceclofenac should be considered in women having difficulties to conceive or undergoing investigations for infertility.

Paracetamol

Epidemiological studies in human pregnancy have shown no effects due to paracetamol used in the recommended dosage. However, paracetamol should be avoided in pregnancy unless considered essential by the physician.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Aceclofenac

Undesirable effects such as dizziness, vertigo, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

Paracetamol

Not known

4.8 UNDESIRABLE EFFECTS

Aceclofenac

Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment.

Aceclofenac is both structurally related and metabolised to diclofenac for which a greater amount of clinical and epidemiological data consistently point towards an increased risk of general arterial thrombotic events (myocardial infarction or stroke, particularly at high doses and in long treatment). Epidemiological data has also found an increased risk of acute coronary syndrome and myocardial infarction associated with the use of aceclofenac.

Gastrointestinal:

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity:

Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular:

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

<u>Other adverse reactions reported less commonly include:</u>

Renal:

Nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome and renal failure.

Hepatic:

abnormal liver function, hepatitis and jaundice.

Neurological and special senses:

Visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological:

Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological:

Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare).

Photosensitivity.

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: 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.

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare/ isolated reports (<1/10,000)**
Blood and lymphatic system disorders			Anaemia	Bone Marrow depression, Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Metabolism and nutrition disorders				Hyperkalemia

Psychiatric disorders				Depression Abnormal dreams Insomnia
Nervous system disorders	Dizziness			Paraesthesia Tremor Somnolence Headache Dysgeusia (abnormal taste)
Eye disorders			Visual disturbance	
Ear and labyrinth disorders				Vertigo Tinnitus
Cardiac disorders			Cardiac failure	Palpitations
Vascular disorders			Hypertension	Flushing Hot flush vasculitis
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm Stridor
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulceration	Melaena Gastrointestinal haemorrhage Gastrointestinal ulceration	Stomatitis Intestinal perforation Exacerbation of Crohn's disease and colitis Ulcerative Haematemesis Gastrointestinal haemorrhage Gastric ulcer Pancreatitis
Skin and subcutaneous tissue disorders		Pruritus Rash Dermatitis Urticaria	Face oedema Angioedema	Purpura Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis) Dermatitis bullous
Musculoskeletal and connective tissue disorders				Cramps in the leg
Renal and urinary disorders		Blood urea increased Blood creatinine increased		Renal insufficiency Nephrotic syndrome Renal failure
Hepatobiliar disorders	Hepatic enzyme increased			Hepatitis Jaundice

				Hepatic injury (including hepatitis) Blood alkaline phosphatase increased
General disorders and administration site conditions				Oedema Fatigue Cramps in legs
Investigations				Weight increase

Paracetamol

Adverse effects of Paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia, neutropenia, pancytopenia, leukopenia and agranulocytosis but these were not necessarily causality related to Paracetamol.

Very rare cases of serious skin reactions have been reported

4.9 OVERDOSAGE

Aceclofenac

There is insufficient data available on the consequences of Aceclofenac in humans.

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure:

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Given the route of administration and the pharmaceutical form, an overdose with injectable Aceclofenac is unlikely.

Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Good urine output should be ensured.

Renal and liver function should be closely monitored. Patients should be observed for at least four

hours after ingestion of potentially toxic amounts. In case of frequent or prolonged convulsions, patients should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures.

Paracetamol

Liver damage is possible in adults who have taken 10g or more of Paracetamol. Ingestion of 5g or more of Paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors:

If the patient

a. Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs than induce liver enzymes.

b. Regularly consumes ethanol in excess of recommended amounts.

c. Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV, starvation, cachexia.

Symptoms

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 poisioning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

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.

Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion

(earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of Paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote decines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with the NPIS or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

Aceclofenac

Pharamcological category: Non-steroidal agent with marked anti-inflammatory and analgesic properties.

ATC code: M01A B16

Mode of action: The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Paracetamol

Pharmacological category: Analgesic, anti-pyretic

ATC code: N02B E01

Mode of action: Paracetamol has analgesic and antipyretic properties but it has no useful anti-inflammatory properties.

Paracetamol's effects are thought to be related to inhibition of prostaglandin synthesis.

5.2 PHARMACOKINETIC PROPERTIES

Aceclofenac

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L.

The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein- bound (>99%). Aceclofenac circulates mainly as unchanged drug. 4'- hydroxyaceclofenac is the main

metabolite detected in plasma. Approximately two- thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites.
No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

Paracetamol

Absorption: paracetamol is readily absorbed from the gastrointestinal tract.

Distribution: peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Metabolism: It is metabolized in the liver. A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause tissue damage.
Elimination: It is excreted in the urine, mainly as the glucuronide and sulphate conjugates. The elimination half-life varies from about 1 to 4 hours.

5.3 PRECLINICAL SAFETY DATA

Not Applicable

6.PHARAMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sr.No.	Excipients	Specifications
1	Maize Starch	BP
2	Microcrystalline Cellulose (Avicel pH 101)	BP
3	Sodium Starch Glycolate	BP
4	Croscarmellose Sodium	BP
5	Povidone (K – 30)	BP
6	Colloidal Anhydrous Silica	BP
7	Purified Talc	BP

8	Sodium Starch Glycolate	BP
9	Croscarmellose Sodium	BP
10	Magnesium Stearate	BP
11	HPMC E-15	BP
12	Propylene Glycol	BP
13	Colour Sunset Yellow Lake	IH
14	**Isopropyl Alcohol	BP
15	**Dichloromethane	BP

BP: British Pharmacopoeia

IHS: IN- House specification

6.2 INCOMPATIBILITY

None such data reported.

6.3 SHELF LIFE

36 months (3 years)

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from direct sunlight and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Mono carton: 1x 10 tablets

Outer carton: 10 x 1x 10 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSABLE AND OTHER HANDLING

None such special precautions for disposing and handling requires for this product.

7. APPLICANT/MANUFACTURER

MANUFACTURER BY:
Head Office Address:

FREDUN PHARMACEUTICALS LIMITED.
26, Manoj Industrial Premises, G. D. Ambekar Marg,
Wadala, Mumbai- 400 031. India

Plant Address:
FREDUN PHARMACEUTICALS LIMITED.
PLOT NO. 14,15,16, ZORABIAN INDUSTRIAL COMPLEX,
VILLAGE VEOOR, TAL. PALGHAR, THANE - 401404,
MAHARASHTRA STATE

APPLICANT NAME:
GENEITH PHARM. LTD.,
NO. 12 ADEWALE CRESCENT,
OFF EWENLA STREET,
OSHODI-APAPA EXPRESSWAY,
OSHODI, NIGERIA.