For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ZULU-P

WARNING: Not for veterinary use.

WARNING : Taking more than daily dose may cause serious liver damage or allergic reactions (e.g. Swelling of the face, mouth and throat, difficulty in breathing, itching or rash).

1. Generic Name

Aceclofenac and Paracetamol Tablets I.P.

2. Qualitative and quantitative Composition:

Each uncoated tablet contains:

Aceclofenac I.P. ……..100 mg
Paracetamol I.P. ……..325 mg
Excipients…….q.s.

The excipients used are Starch, Betacyclodextrin, Polyvinyl Pyrrolidone, Sorbitol, Microcrystalline Cellulose, Talc, Colloidal Silicon Dioxide and Magnesium Stearate.

3. Dosage form and strength

Dosage form: Uncoated tablet

Strength: Aceclofenac 100 mg and Paracetamol 325 mg

4. Clinical particulars

4.1. Therapeutic indication

For acute painful conditions in adults only.

4.2. Posology and method of administration

Posology

Dosage: As directed by the Physician.

It is recommended that the FDC of aceclofenac and paracetamol should be administered under the supervision of physicians only.

Adults: The daily recommended dose is one tablet daily for adults.

Paediatric population: There are no clinical data on the use of aceclofenac in children and therefore it is not recommended for use in children.

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.

Renal insufficiency: There is no evidence that the dosage 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 medication should be reduced in patients with hepatic impairment.

Method of administration

The tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake. Never change the dose of your medicine without talking to your doctor first.

4.3. Contraindications

Hypersensitivity to the active substance Aceclofenac and Paracetamol, or to any of the other excipients.

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

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

Hepatic failure and renal failure.

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

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

Active bleedings or bleeding disorders.

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.

4.4. Special warnings and precautions for use

WARNING:

- Not for veterinary use.
- Taking more than daily dose may cause serious liver damage or allergic reactions (e.g. Swelling of the face, mouth and throat, difficulty in breathing, itching or rash).

Aceclofenac

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (GI and cardiovascular risks below).

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 or recovering from major surgery, and the elderly. The importance of prostaglandins in maintaining renal blood flow should be taken into account in these patients. Renal function should be monitored in these patients.

Renal:

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.

Use of Aceclofenac 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. Patients with congestive heart failure (NYHA-I) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with aceclofenac after careful consideration. 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 a history of cerebrovascular bleeding.

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 gastrointestinal 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, or haematological abnormalities, as these conditions may be exacerbated.

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.

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

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:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs.

Hypersensitivity reactions:

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Haematological:

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

Long-term treatment:

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

Paracetamol

Prolonged or frequent use is discouraged. Patients should be advised not to take other Paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In children treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatocellular insufficiency (including Gilbelt's syndrome), severe hepatic insufficiency (Child-Pugh >9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6- phosphatedehydrogenase deficiency, haemolytic anaemia, dehydration. alcohol abuse and chronic malnutrition.

The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2000 mg in such case.

Alcohol should not be used during the treatment with Paracetamol.

"Caution is advised in asthmatic patients sensitive to aspirin, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported in less than 5% of the patients tested"

Abrupt discontinuation of long term use of high-dosed analgesics, taken not as directed, may cause headache, tiredness, muscular pain, nervousness and vegetative symptoms. The withdrawal symptoms subside within a few days. Patients should be advised to consult their doctor if headaches become persistent.

Paracetamol Effervescent Tablets should not be administered in children and adolescents below 16 years of age and under 50 kg body weight.

This medicinal product contains 438 mg of sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

Do not exceed the stated dose.

If symptoms persist consult a doctor.

Treatment with an antidote is advised if an overdose is suspected.

4.5. Drugs interactions

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 including GI bleeding.

Anti-hypertensives: NSAIDs, may reduce the effect of activity antihypertensives. The risk of acute renal insufficiency 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: Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. 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 like digoxin: NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and inhibit the renal clearance of glycosides, resulting in increased plasma glycoside levels. The combination should be avoided unless frequent monitoring of glycoside levels can be performed.

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

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 both an NSAID 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.

Ciclosporin, Tacrolimus: Administration of NSAID drugs together with ciclosporin or tacrolimus is thought to increase the risk of nephrotoxicity 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 are indications 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 with 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.

Paracetamol

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The metabolization of paracetamol is increased in patients taking enzyme-inducing drugs such as rifampicin and some antiepileptics (carbamazepine, phenytoin, phenobarbital, primidone). Isolated reports describe unexpected hepatotoxicity in patients taking enzyme-inducing drugs and alcohol.

• Probenecid causes an almost 2-fold reduction in clearance of Paracetamol by inhibiting its conjugation with glucuronid acid. A reduction of the Paracetamol dose should be considered for concomitant treatment with probenecid.

• Salicylamide may prolong the elimination t1/2 of Paracetamol.

• Metoclopramide and donperidone accelerate absorption of Paracetamol.

• Cholestyramine reduces absorption of Paracetamol and therefore should not be administered within an hour following Paracetamol administration.

• Concomitant use of Paracetamol (4000 mg per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.

• Isoniazid: Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver.

• Lamotrigine: decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of liver metabolism.

Interference with laboratory tests:

Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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/fetal 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. 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 and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

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

Breast-feeding

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

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.

Paracetamol

Pregnancy:

A large amount of reported data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Lactation:

In reported data Paracetamol/ metabolites are excreted in human milk, but at therapeutic doses of Paracetamol 1000 mg Effervescent Tablets no effects on the breastfed newborns/infants are anticipated.

Paracetamol can be used during breast-feeding.

Fertility:

There are no or limited reported amount of data from the influence of Paracetamol.

4.7. Effects on ability to drive and use machines

Undesirable effects such as dizziness, vertigo, drowsiness, fatigue, visual disturbances or other central nervous system disorders are possible after taking NSAIDs. If affected, patients should not drive or operate machinery. Paracetamol has no influence on the ability to drive and use machines.

4.8. Undesirable effects

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 and cerebrovascular: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

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

Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment Other adverse reactions reported less commonly include:

Renal: interstitial nephritis

Neurological and special senses: optic neuritis, 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, confusion, hallucinations, malaise, and drowsiness.

Haematological: agranulocytosis, aplastic anaemia

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

If serious adverse reactions occur, Aceclofenac tablets should be withdrawn.

The following is a table of adverse reactions reported during clinical studies and after authorisation, grouped by System OrganClass and estimated frequencies. 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).

MedDRa SOC	**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**
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 Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased			Hepatic injury (including hepatitis) Jaundice Blood alkaline phosphatase increased
Skin and subcutaneous tissue disorders		Pruritus Rash Dermatitis Urticaria	Angioedema	Purpura Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis)
Renal and urinary disorders		Blood urea increased Blood creatinine increased		Renal failure Nephrotic syndrome
General disorders and administration site conditions				Oedema Fatigue Cramps in legs
Investigations				Weight increase

Paracetamol

The frequency using the following convention should be: 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.

Frequency	**Symptoms**	**System**

Rare >1/10000 - < 1/1000	Platelet disorders, stem cell disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic, naemia, pancytopenia	Blood and lymphatic system disorders
	Allergies (excluding angioedema).	Immune system disorders
	Depression NOS, confusion, hallucinations.	Psychiatric disorders
	Tremor NOS, headache NOS.	Nervous system disorders
	Abnormal vision.	Eye disorders
	Cardiac Oedema	Cardiac disorders
	Haemorrhage NOS, abdominal pain NOS, dianhoea NOS, nausea, vomiting.	Gastrointestinal disorders
	Abnormal Hepatic function, hepatic failure, hepatic necrosis jaundice.	Hepato-biliary disorders
	Pruritus, rash, sweating, purpura, angioedema, urticaria	Skin and subcutaneous tissue disorders
	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.	General disorders and administration conditions site conditions
	Overdose and poisoning	Injury, poisoning and procedural complications
Very Rare (< 10,000)	Bronchospasm	Respiratory, thoracic and mediastinal disorders
	hepatotoxicity	Hepato-biliary disorders
	Hypersensitivity reaction (requiring discontinuation of treatment)	General disorders and administration site conditions
	Hypoglycemia	Metabolism and nutrition disorders
	Sterile pyuria (cloudy urine) and renal side effects	Renal and urinary disorders

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis. Stevens Johnson syndrome, erythema multiforme, edema of the larynx, anaphylactic shock. anemia. liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastro intestinal effects and vertigo have been reported.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9. Overdose

Aceclofenac

Symptoms:

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting and 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 lifethreatening overdose.

Specific therapies such as, dialysis or haemoperfusion are probable 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 oral aceclofenac essentially consists of supportive and symptomatic measures for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression.

Paracetamol

There is a risk of poisoning, particularly in elderly subjects, in young children. In patients with liver disease, in cases of chronic alcoholism and in patients with chronic malnutrition. Overdose of Paracetamol is potentially fatal in all populations.

Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor, and abdominal pain. Immediate emergency measures are necessary in case of paracetamol overdose, even when no symptoms are present.

• Overdose, 10g or more of Paracetamol in adults or 150 mg/kg of body weight, causes liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, AL T), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Emergency Procedure:

• Immediate transfer to hospital.

• Blood sampling to determine initial paracetamol plasma concentration.

• IV (or oral if possible) administration of the antidote N-acetylcysteine as soon as possible or within 8 hours of the overdose.

• Activated charcoal may be used if the dose of Paracetamol ingested exceeds 12g or 150 mg/kg and should be undertaken if within 1 hour of the overdose.

• Oral methionine is also effective provided that it is given within 10 to 12 hours of the overdose.

• Symptomatic treatment should be implemented.

• Haemodialysis or haemoperfusion is possible in cases of severe poisoning.

5. Pharmacological properties

5.1. Mechanism of Action

Aceclofenac

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

Analgesic – the mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation. Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependant on the inhibition of prostaglandin synthesis. This inhibition appears, however to be on a selective basis.

5.2. Pharmacodynamic properties

Aceclofenac

Pharmacotherapeutic group: nonsteroidal anti-inflammatory drug (NSAID), Acetic acid derivatives and related substances

ATC code: M01A B16

Aceclofenac is a non-steroidal agent with marked anti-inflammatory and analgesic properties.

Paracetamol

Pharmacotherapeutic group: Anilides
ATC Code: N02BE01

Pharmacodynamic effects: Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependant on the inhibition of prostaglandin synthesis. Analgesic – the mechanism of analgesic action has not been fully determined.

5.3. 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

The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood. saliva and plasma. Protein binding is low.

Metabolism

Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucoronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours. principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.

Elimination half-life is about 2 hours.

Special patient groups

Renal Insufficiency: in cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly Subjects: the capacity for conjugation is not modified.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Aceclofenac

The results from preclinical studies conducted with aceclofenac are consistent with those expected for NSAIDs. The principal target organ was the gastro-intestinal tract.

No unexpected findings were recorded.

Aceclofenac was not considered to have any mutagenic activity in three in vitro studies and an in vivo study in the mouse.

Aceclofenac was not found to be carcinogenic in either the mouse or rat.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some fetuses.

Paracetamol

In reported animal studies investigating the acute. sub chronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and necrosis were observed. These changes are, on the one hand. attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites that is

probably responsible for the toxic effects and the corresponding organic changes have also been found in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of maximum therapeutic doses. At subtoxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

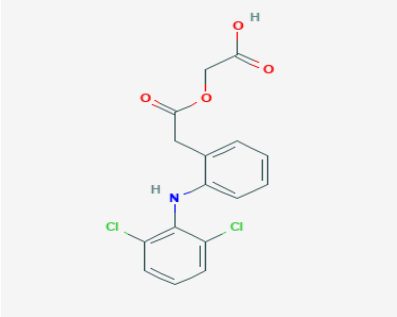
Long-term studies in rats and mice yielded no evidence on relevant carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Paracetamol crosses the placental barrier. In reported animal studies and clinical experience to date have not indicated any teratogenic potential.

7. Description

Aceclofenac

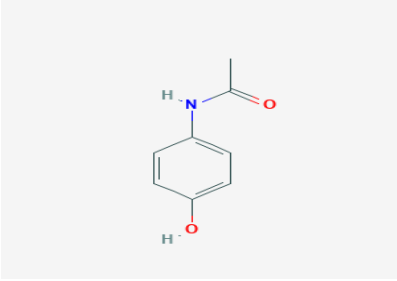
Aceclofenac is 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid having empirical formula $C_{16}H_{13}Cl_2NO_4$ and molecular weight is 354.2. The chemical structure is:



Aceclofenac is white or almost white, crystalline powder which is freely soluble in acetone; soluble in ethanol (95%); practically insoluble in water.

Paracetamol

Paracetamol is 4-hydroxyacetanilide having molecular formula of $C_8H_9NO_2$ and molecular weight is 151.2 and the chemical structure is:



Paracetamol is white crystals or white, crystalline powder which is freely soluble in ethanol (95%) and in acetone; sparingly soluble in water; very slightly soluble in dichloromethane and in ether.

Aceclofenac and Paracetamol Tablets are white to off-white, capsule shaped biconvex, uncoated tablets plain on both sides. The excipients used are Starch, Betacyclodextrin, Polyvinyl Pyrrolidone, Sorbitol, Microcrystalline Cellulose, Talc, Colloidal Silicon Dixoide and Magnesium Stearate.

8. Pharmaceutical particulars

8.1. Incompatibilities

There's no information available.

8.2. Shelf-life

Store protected from light & moisture, at a temperature not exceeding 30°C.

8.3. Packaging information

ZULU-P is packed in blister strips of 10 tablets.

8.4. Storage and handing instructions

Dosage: As directed by the Physician.

Keep all the medicines out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Manufactured by:

Pure & Cure Healthcare Pvt. Ltd.

Plot No.: 26A, 27-30, Sector – 8A, I.I.E., SIDCUL, Ranipur, Haridwar-249403 (Uttarakhand).

11. Details of permission or licence number with date

Mfg Licence No.: 31/UA/2013 issued on 14.05.2024

12. Date of revision

MAR 2026

MARKETED BY

TORRENT PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/ZULU-P/100, 325 mg/MAR 2026/04/PI