"To be sold by retail on the prescription of R.M.P. only"

AROFF PLUS

1. Generic Name

Aceclofenac & Paracetamol Tablets

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

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

The daily recommended dose is one tablet daily for adults.

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 impairment

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 impairment

There is some evidence that the dose of medication should be reduced in patients with hepatic impairment.

Method of administration

The film-coated 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 nonsteroidal anti-inflammatory drugs.

Hepatic failure and renal failure.

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 (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').

Paracetamol

Underlying liver disease increases the risk or paracetamol related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

Patients should be advised to consult their doctor if their headaches become persistent.

Patients should be advised to consult a doctor if they suffer from non-serious arthritis and need to take painkillers every day.

Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol may increase the risk of metabolic acidosis. Use with caution in patients with glutathione depletion due to metabolic deficiencies.

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

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

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 and Breast-feeding

Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy if clinically needed, however, as with any medicine it should be used at the lowest effective dose for the shortest possible time.

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

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.

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.

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	Flatulence Gastritis Constipation Vomiting	Melaena Gastrointestinal haemorrhage	Stomatitis Intestinal perforation
	Diarrhoea	Mouth ulceration	Gastrointestinal ulceration	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

Adverse events of paracetamol from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class and frequency.

The following convention has been utilised for the classification of the undesirable effects: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from available data):

Body System	Undesirable effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia Agranulocytosis	Very rare
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes and angioedema. Very rare cases of	Very rare
	Serious skin reactions have been reported.	
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

Aceclofenac

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 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

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

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

1, Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or 2, Regularly consumes ethanol in excess of recommended amounts.

Or 3, Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol over-dosage 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 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.

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 declines sharply after this time. If required the patient should be given intravenous Nacetylcysteine, 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 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

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The concentration in plasma reaches a peak in 30 to 60 minutes and the plasma half-life is 1 - 4 hours after therapeutic doses.

Paracetamol is relatively uniformly distributed throughout most body fluids. Binding of the drug to plasma proteins is variable; 20 to 30% may be bound at the concentrations encountered during acute intoxication. Following therapeutic doses 90 - 100% of the drug may be recovered in the urine within the first day. However, practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation. 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 over-dosage and cause liver damage.

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.

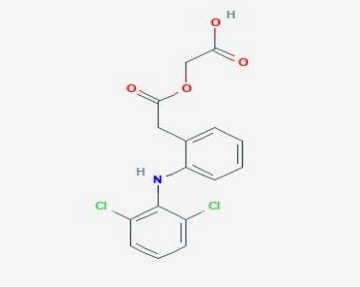
Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some fetuses.

Paracetamol

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

7. Description Aceclofenac

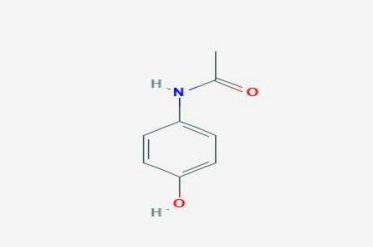
Aceclofenac is 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid having empirical formula C16H13Cl2NO4 and molecular weight is 354.2. The chemical structure is:



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 C8H9NO2 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

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

AROFF PLUS is packed in blister strips of 10 tablets.

8.4 Storage and handing instructions

Store in a dry place at a temperature not exceeding 25°C.

Keep all the medicines out of reach of children.

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.**

Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What AROFF PLUS is and what it is used for

AROFF PLUS contains the active substance Aceclofenac and Paracetamol.

AROFF PLUS is used for the treatment of acute painful conditions in adults only.

9.2 What you need to know before you take AROFF PLUS

Do not take AROFF PLUS:

– if you are allergic to Aceclofenac & Paracetamol, or to any of the other ingredients of this medicine.

– if you have taken aspirin or any other NSAIDs and experienced one of the following:
- asthma attack causing tightness in the chest wheezing and difficulty breathing.
- runny nose, itching and/or sneezing (irritation of the nose).
- raised red circular patchy rash on the skin which may have felt itchy or like a sting or burn.
- severe allergic reaction known as anaphylactic shock. The symptoms may be life threatening and include difficulty breathing, wheezing, abdominal pain and vomiting.

– if you have a history of, suffer from, or suspect that you have a stomach ulcer or have vomited blood or passed blood in your faeces (black tarry stools).

– if you have severe kidney disease

– if you are pregnant (unless your doctor considers it essential for you to continue to take this medicine)

Warnings and precautions

Talk to your doctor before taking AROFF PLUS:

- if you suffer from any other form of kidney or liver disease.
- if you have any of the following disorders, as they may worsen:
    - Disorders of the stomach or gut/bowel
    - inflammatory bowel disease (ulcerative colitis)
    - chronic inflammatory bowel disease (Crohn's disease)
    - ulceration, bleeding or perforation of the stomach or bowel

- if you have, or have ever had problems with the circulation of the blood to your brain.
- if you suffer from asthma or any other breathing problems.
- if you suffer from a rare inherited disorder known as porphyria.
- if you smoke
- if you have diabetes
- if you have angina, blood clots, high blood pressure, raised cholesterol or other raised body fats such as triglycerides –if you regularly drink alcohol
- –if you have a severe infection as this may increase risk of metabolic acidosis

Children

The use of AROFF PLUS is not recommended for infants and children.

Other medicines and AROFF PLUS

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including those obtained without a prescription.

Tell your doctor if you are taking the following medicines before starting AROFF PLUS:

– medicines used to treat mental health problems like depression (selective serotonin-reuptake inhibitors (SSRIs) such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) or manic depression (lithium).

– medicines used to treat heart failure and irregular heart beats (cardiac glycosides such as digoxin)

– medicines used to treat high blood pressure (antihypertensives: ACE inhibitors such as enalopril, lisinopril; angiotensin II receptor antagonists such as losartan, candesartan; also hydralazine, methyldopa, clonidine, moxonidine, propranalol)

– medicines to treat infection (quinolone antibiotics such as ciprofloxacin, ofloxacin, levofloxacin moxifloxacin)

– drugs used to increase the rate of urine excretion (diuretics such as thiazides,furosemide amiloride hydrochloride)

– medicines that stop blood clotting (anticoagulants) such as warfarin, heparin

– methotrexate which is used to treat cancer and autoimmune disorders such as arthritis and skin conditions

– mifepristone

– any other painkiller NSAID drugs (aspirin, ibuprofen, naproxen, COX-2 inhibitors such as celecoxib and etoricoxib)

– antiplatelet drugs such as clopidogrel

– metoclopramide or domperidone or colestyramie or warfarin

AROFF PLUS with food, drink and alcohol

AROFF PLUS must be taken preferably with or after food.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take AROFF PLUS if you are pregnant or think you are pregnant. The safety of this medicine for use during pregnancy is not known.

AROFF PLUS should not be used if you are breast-feeding. It is not known if this medicine passes into breast milk. It is not recommended for use during breast-feeding unless considered essential by your doctor.

Driving and using machines

If you are taking AROFF PLUS and you experience dizziness, drowsiness, vertigo, tiredness or any difficulty with your eyesight, you must not drive or use machinery.

9.3 How to take AROFF PLUS

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one tablet per day.

Method of administration: The uncoated tablet must be taken orally, swallowed whole should be taken with or after food. It is recommended to take the daily dose in one single intake. Do not crush or chew the tablets.

Special dosage instructions for specific populations: **Elderly**

If you are elderly, you are more likely to experience serious side effects.

If you take more AROFF PLUS than you should

Tell your doctor or pharmacist if you have taken more than the recommended dose. If possible take your medicine and this leaflet with you.

If you forget to take AROFF PLUS

Do not take a double dose to make up for the forgotten dose. Take your next, normal dose, the next day, at your usual time.

If you have any further questions on the use of this medicine ask your doctor or pharmacist.

9.4 Possible side effects

Aceclofenac

Like all medicines, this medicine can cause side effects, although not everybody gets them. Stop taking the medicine and seek medical advice IMMEDIATELY, if you experience any of the following side effects,

– Severe allergic reaction (anaphylactic shock). Symptoms may develop quickly and can be life threatening if not immediately treated and include fever, difficulty breathing, wheezing, abdominal pain, vomiting, swelling of the face and throat.

– Severe skin rashes such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. These are potentially life-threatening and develop quickly forming large blisters and the skin to peel away. The rash can also appear in the mouth, throat or eyes. Fever, headache and aching of the joints usually occur at the same time.

– Meningitis. The symptoms include high fever, headache, vomiting, blotchy red rashes, neck stiffness, sensitivity and intolerance to light.

– passing blood in your faeces (stools/motions).

– passing black tarry stools. Vomit any blood or dark particles that look like coffee grounds.

– kidney failure.

Stop taking the medicine and seek medical advice if you experience: indigestion

or heartburn

abdominal pain (pains in your stomach) or other abnormal stomach symptoms

If any of the below side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common (may affect up to 1 in 10 people):

- dizziness
- nausea (feeling sick)
- diarrhoea
- increased liver enzymes in the blood

Uncommon (may affect up to 1 in 100 people):

- wind
- inflammation or irritation of the lining of the stomach
- constipation
- vomiting
- mouth ulcers
- itching
- rash
- inflammation of the skin

- raised circular red itchy, stinging or burning patches on the skin (hives)
- increase in blood urea levels
- increase in blood creatinine levels

Rare (may affect up to 1 in 1,000 people):

- hypersensitivity (allergic reaction)
- problems with eyesight
- heart failure
- high blood pressure shortness of breath
- bleeding from the stomach or bowel
- stomach or bowel ulceration

Very Rare (may affect up to 1 in 10,000 people):

- depression
- strange dreams
- inability to sleep
- tingling, pricking or numbness of skin
- uncontrollable shaking
- drowsiness
- headaches
- abnormal taste in the mouth
- sensation of spinning when standing still
- ringing in the ears
- heart pounding or racing hot flushes
- difficulty breathing
- high pitched noise when breathing
- inflammation of the mouth
- perforation of either the stomach, large intestine or bowel wall
- worsening of colitis and Crohn’s disease
- inflammation of the pancreas injury of the liver (including hepatitis)
- yellowing of the skin (jaundice)
- spontaneous bleeding into the skin (appears as a rash)
- nephrotic syndrome: a condition which indicates kidney damage and includes large amounts of protein in the urine, low blood albumin levels, high blood cholesterol levels and swelling of the legs, feet or ankles water retention and swelling
- tiredness
- leg cramps

- increased blood alkaline phosphatase levels
- weight gain

Other side effects that have been reported with this type of drug (NSAIDs) are:

- hallucinations
- confusion
- blurred, partial or complete loss of vision
- painful movement of the eye
- worsening of asthma
- skin reaction to sunlight
- inflammation of the kidneys
- generally feeling unwell

Paracetamol

A small number of people have had side effects. Very rare cases of serious skin reactions have been reported.

Stop taking medication if you experience:

– Allergic reaction which may severe such as skin rash and itching sometimes with swelling of the mouth or face or shortness of breath

– Skin rash or peeling or mouth ulcers

– Breathing problem

– Unexplained bruising or bleeding

– Nausea, yellowing of the eyes and skin

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store AROFF PLUS

Store in a dry place at a temperature not exceeding 25°C.

9.6 Contents of the pack and other information

What **AROFF PLUS** contains

The active substances **AROFF PLUS** is Aceclofenac and Paracetamol.

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

10. Details of manufacturer

Manufactured by:
Torrent Pharmaceuticals Ltd.
32 No. Middle Camp, NH-10,
East District, Gangtok, Sikkim – 737135.

11. Details of permission or licence number with date

Mfg. Lic. No. : M/563/2010 issued on 04.02.2019

12. Date of revision

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TORRENT PHARMACEUTICALS LTD.

IN/AROFF PLUS/100, 325 mg/APR-21/02/PI