For the use of a Registered Medical Practitioner/ Hospital/ Laboratory Only

Aceclofenac and Paracetamol Tablets IP

Aceflick™ P
Tablets

Smartdose™ Technology

COMPOSITION
Each uncoated tablet contains :
Aceclofenac IP 100 mg Paracetamol IP 325 mg Colour : Sunset Yellow FCF

PHARMACEUTICAL FORM Uncoated tablet

THERAPEUTIC INDICATION
It is indicated for the treatment of acute painful condition in adults only.

POSOLOGY AND METHOD OF ADMINISTRATION
The recommended dose is 1 - 2 tablets 2 times in a day or as directed by the physician.
Method of administration: For oral administration only.
Patients should be advised to swallow the tablet whole, not be chewed or crushed and to be taken with sufficient amount of liquid (water).

CONTRAINDICATIONS
It is contraindicated in patients with known hypersensitivity to any of the active substance (s) or to any of the excipients.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- NSAIDs are contraindicated in the 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.
- Aceclofenac and paracetamol 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.
- Patients with a history of, or active, gastro-intestinal ulcers, bleeding or perforation (two or more distinct episodes of proven ulceration or bleeding).
- Severe hepatic failure or renal failure and heart failure.
- During the last trimester of pregnancy.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy and acute porphyria.

SPECIAL WARNINGS AND PRECAUTIONS OF USE
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 importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. 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 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 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 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, and 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, with a history suggestive of gastro-intestinal ulceration, 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.
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: 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. Patients appear to be at highest risk for 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.
Impaired female fertility: The use of aceclofenac 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 should be considered. Hypersensitivity reactions:
As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Haematological: Aceclofenac may reversibly inhibit platelet aggregation.
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 should be given with care to patients with impaired kidney or liver function. It should also be given with care to patients with alcohol dependence.
Precautions
Renal: Patients with renal, cardiac or hepatic impairment, a history of hypertension and the elderly, should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or other products that can significantly impact renal function, or those recovering from major surgery. Effects on renal function are usually reversible on withdrawal of diclofenac sodium.
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), diclofenac sodium should be discontinued. Hepatitis may occur without prodromal symptoms.
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.

DRUG 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.
Antihypertensives: Reduced antihypertensive effect. 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: 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, e.g. Digoxin: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels. The combination should be avoided unless frequent monitoring of glycoside levels can be performed.
Lithium: Several NSAIDs drugs inhibit the renal clearance of lithium, resulting in increased serum concentration 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 kept in mind even 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 to12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
Corticosteroids: Increased risk of GI ulceration or bleeding
Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin. Close monitoring of patients on combined anticoagulants and aceclofenac 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.
Antiplatelet Agents and SSRIs: Increased risk of GI bleeding.
Cyclosporine, Tacrolimus: Administration of NSAID drugs together with cyclosporine or tacrolimus is thought to increase the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidneys. During combination therapy, it is, therefore, important to carefully monitor renal function.
Zidovudine: Increased risk of haematological toxicity is present 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, 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
Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.
Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
Warfarin: The anticoagulant 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.
Chloramphenicol: Increased plasma concentration of chloramphenicol.

USE IN SPECIAL POPULATIONS Aceclofenac
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. The regular use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child.
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. 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 foetuses.
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding. The use of aceclofenac should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.
Paracetamol
Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of the doctor regarding its use. Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

EFFECTS ON ABILITY TO DRIVE AND OPERATE HEAVY MACHINERY
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. Based on the Pharmacodynamic properties and the adverse events profile.

ADVERSE DRUG REACTIONS
The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are gastrointestinal disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional occurrence of dizziness. Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment; and dermatological complaints including pruritus and rash.
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. 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).
Investigations: Abnormal hepatic enzyme and serum creatinine levels have also been reported.
Other adverse reactions reported less commonly include:
Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic 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.

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.If serious adverse reactions occur, aceclofenac should be withdrawn.
Paracetamol
Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia purpura, methaemoglobenaemia and agranulocytosis, but these were not necessarily causality related to paracetamol.
Reporting of side effects or suspected adverse reaction: If you get or experience any side effects, talk to your doctor or pharmacist or report to indiadrugsafety@akums.in. You can also report side effects directly via the National Pharmacovigilance Program of India by calling on 18003133363. By reporting side effects, you can help provide more information on the safety of this product.

OVERDOSE
Risk factors: **If the patient:**
is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's wort or other drugs that induce liver enzymes, or
is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.
Immediate treatment is essential in the management of overdosage. Despite a lack of significant early symptoms, patients should be referred to a hospital urgently for immediate medical attention.
Symptoms include headache, pallor, nausea, vomiting, epigastric pain, GI irritation, GI bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally convulsions, anorexia and abdominal pain. In cases of significant poisoning, acute renal failure and liver damage are possible.
Abnormalities of glucose metabolism and metabolic acidosis may occur.
In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported. Patients should be treated symptomatically as required. Within 1 hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within 1 hour of ingestion of a potentially life-threatening overdose. Administration of oral methionine or intravenous N-acetylcysteine, which may have a beneficial effect up to at least 48 hours after the overdose, may be required. General supportive measures must be available.
Specific therapies such as 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 4 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.
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PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties Aceclofenac
Aceclofenac, is a non-steroidal agent with anti-inflammatory and analgesic properties. The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis.
Aceclofenac is a potent inhibitor of the enzyme, COX, which is involved in the production of prostaglandins. Aceclofenac relieves pain and inflammation through a variety of mechanisms and, in addition, exerts stimulatory effects on cartilage matrix synthesis.
It inhibits various mediators of pain and inflammation, including the following:
PGE2 via COX inhibition (COX-1 and COX-2) after intracellular metabolism to 4-hydroxyaceclofenac and diclofenac in human rheumatoid synovial cells and other inflammatory cells.
IL-1beta, IL-6 and tumour necrosis factor-alpha in human osteoarthritic synovial cells and human articular chondrocytes.
Reactive oxygen species (which plays a role in joint damage) has
also been observed in patients with OA of the knees.
Expression of cell adhesion molecules (which is implicated in cell migration and inflammation) has also been shown in human neutrophils.
Stimulatory Effects on Cartilage Matrix Synthesis: Aceclofenac stimulates glycosaminoglycan synthesis in human osteoarthritic cartilage by inhibition of IL-1beta and suppresses cartilage degeneration by inhibiting IL-1beta-mediated promatrix metalloproteinase production and proteoglycan release.
Paracetamol
Paracetamol produces analgesic and antipyretic as main effects and it has been also reported that paracetamol has a weak anti-inflammatory effect. Analgesic action: The central analgesic action of Paracetamol resembles that of aspirin. It produces analgesia by raising pain threshold. Antipyretic effect: The antipyretic effect of Paracetamol is attributed to its ability to inhibit COX in the brain where peroxide tone is low. Recent evidence suggests inhibition of COX-3 (believed to be splice variant product of the COX-1 gene) could represent a primary central mechanism by which Paracetamol decreases pain and possibly fever.
Pharmacokinetic properties Aceclofenac *Absorption*
After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25-3.00 hours following ingestion.
Distribution
Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L. Aceclofenac is highly protein-bound (>99%). Aceclofenac circulates mainly as unchanged drug.
Metabolism
4-hydroxyaceclofenac is the main metabolite detected in plasma.
Elimination
The mean plasma elimination half-life is around 4 hours. Approximately two- thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites.
Paracetamol
Paracetamol is rapidly and almost completely absorbed from gastrointestinal tract with peak plasma concentrations (Cmax) occurring about 10 to 60 minutes after oral administration.
Plasma protein binding is negligible at usual therapeutic concentration but increases with increasing concentrations. Acetaminophen is distributed throughout most body fluids. The plasma half-life (t1/2) 1-4 hours and the effect after oral dose lasts for 3-5 hours. Paracetamol is metabolized primarily in liver and excreted in the urine mainly as glucuronide and sulfate conjugate.

INCOMPATIBILITY Not applicable.

PACKAGING INFORMATION As per carton

STORAGE INSTRUCTIONS
Store protected from moisture, at a temperature not exceeding 30°C.

Warning : Not for veterinary use.

Manufactured by: Pure & Cure Healthcare Pvt. Ltd.
(A subsidiary of **Akums Drugs & Pharmaceuticals Ltd.**)
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