For the use of a Registered Medical Practitioner only.

1. GENERIC NAME AND BRAND NAME
Aceclofenac and Paracetamol Tablets I.P.
Nicoace™ - Plus

Aceclofenac

Cardiovascular Risk

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.) Aceclofenac is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

Paracetamol
Warning:
Taking more than daily dose of paracetamol may cause serious liver damage or allergic reactions such as swelling of the face, mouth and throat, difficulty in breathing, itching or rash.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains:
Aceclofenac I.P. 100 mg
Paracetamol I.P. 325 mg
Colour: Yellow Oxide of Iron & Titanium Dioxide I.P.

3. DOSAGE FORM AND STRENGTH
Kindly refer section 1 and 2

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATION
For acute painful conditions in adults only.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
The recommended dose is 1 tablet twice daily with or after food.

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to Aceclofenac, Paracetamol or to any of the excipients of the product.
- Hypersensitivity to aspirin or other NSAIDs, precipitate attacks of bronchospasm, acute rhinitis or urticaria.
- Patients with active or suspected peptic ulcer or gastrointestinal bleeding or bleeding disorders.
- Patients with severe heart failure, hypertension, hepatic or renal insufficiency
- Third trimester of pregnancy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

1. Elderly

Increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal have been observed with elderly patients.

2. Gastrointestinal bleeding, ulceration and perforation

At any time during treatment, GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, with or without warning symptoms or a previous history of serious GI events. The risk of these disorders is higher with increasing NSAID dose, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. Treatment should be commenced in these patients with lowest dose available. Any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment in patients with a history of GI toxicity, particularly when elderly, should be reported. Caution should be advised in patients receiving concomitant medications such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin which could increase the risk of ulceration or bleeding.

3. Hepatic

Close medical supervision is required in patients suffering from severe impairment of hepatic function.

4. Renal

Since the use of NSAIDs may result in deterioration of renal function, patients with mild renal or cardiac impairment and the elderly should be kept under supervision. The therapy should be started at the lowest effective dose and renal function should be monitored regularly. Effects on renal function are usually reversible on withdrawal of Aceclofenac.

5. Haematological

Aceclofenac may reversibly inhibit platelet aggregation.

6. Cardiovascular and cerebrovascular effects

Fluid retention and oedema have been reported in association with NSAID therapy. Hence, monitoring and medical surveillance are required for patients with a history of hypertension and/or mild to moderate congestive heart failure. Aceclofenac should be given to patients with

uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease only after careful consideration. Similar consideration should be made when long term therapy has to be initiated in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

7. Long-term treatment:

All patients who are receiving NSAIDs should be monitored as a precaution for renal failure, impaired hepatic function and change in blood counts. Caution is advised in patients suffering from or with a history of bronchial asthma as NSAIDs cause bronchospasms.

Rare cases of serious skin reactions, some of them fatal, including exfolitative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported with the use of NSAIDs. Onset of these reactions occur in the majority of cases within the first month of treatment as patients are at highest risk of these reactions early in the course of therapy. Discontinue aceclofenac at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

8. Alcohol dependence

Use paracetamol with caution in alcohol-dependent patients

Other

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

4.5 DRUG INTERACTIONS

No.	Drug	Drug Interaction	Remark
1.	Lithium	Aceclofenac may increase plasma concentrations of lithium	
2.	Cardiac Glycosides	NSAIDs may increase plasma glycoside (including digoxin) levels, through their renal effects exacerbate cardiac failure and reduce the glomerular filtration rate in patients receiving glycosides	Caution should be exercised while administrating glycosides with Aceclofenac
3.	Diuretics	Aceclofenac may inhibit the activity of diuretics, diuretics can increase the risk of nephrotoxicity of NSAIDs	When concomitant administration of aceclofenac with potassium-sparing diuretics is employed, serum potassium should be monitored

4.	Anticoagulants	Aceclofenac may enhance the activity of anticoagulants such as warfarin	Close monitoring of patients on combined anticoagulant and Aceclofenac therapy should be done
5.	Antidiabetic agents	Isolated reports of hypoglycaemic and hyperglycaemic effects with diclofenac	Dosage adjustment should be considered while giving hypoglycaemic agents with aceclofenac
6.	Methotrexate	NSAIDs may increase plasma levels, resulting in increased toxicity	Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other
7.	Mifepristone	NSAIDs can reduce the effect of mifepristone	NSAIDs should not be used for 8-12 days after mifepristone administration
8.	Corticosteroids	Increased risk of gastrointestinal ulceration or bleeding with Aceclofenac	
9.	Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)	Increased risk of gastrointestinal bleeding with Aceclofenac	
10.	Ciclosporin	Due to the effect of NSAIDs on renal prostaglandins, Ciclosporin nephrotoxicity may be increased	
11.	Quinolone antimicrobials	Convulsions may occur due to an interaction between quinolones and NSAIDs which may occur in patients with or without a previous history of epilepsy or convulsions	Caution should be exercised for concomitant administration of a quinolone and NSAID.
12.	Cholestyramine	Reduced absorption of cholestyramine within one hour of administration with paracetamol	
13.	Metoclopramide	Accelerated absorption of ???with metoclopramide	
14.	Barbiturates, carbamazepine, hydantoins, rifampicin and sulfinpyrazone	Potentially fatal: Increased risk of toxicity with other hepatotoxic drugs or drugs which induce microsomal enzymes Decreased effect of paracetamol with barbiturates, carbamazepine,	

		hydantoins, rifampicin and sulfinpyrazone,	
15.	Warfarin	Paracetamol may increase effect of warfarin	
16.	Chronic alcoholics	Paracetamol increases the risk of liver damage in chronic alcoholics	

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

1. Pregnancy and lactation

Aceclofenac containing products should not be used in pregnant and lactating women. Caution should be exercised when acetaminophen is administered to a nursing woman.

Paracetamol is a Pregnancy Category C drug . There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Acetaminophen should be given to a pregnant woman only if clearly needed.

Caution should be exercised when acetaminophen is administered to a nursing woman

2. Geriatric

Use aceclofenac containing products with caution in elderly. May lead to increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation in elderly which may be fatal..

With paracetamol treatment , no overall differences in safety or effectiveness were observed between older patients and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

3. Paediatric

Use with caution in children. The safety and effectiveness of acetaminophen for the treatment of acute pain and fever in paediatric patients ages 2 years and older is supported by evidence from adequate and well controlled studies of acetaminophen in adults. The effectiveness of acetaminophen for the treatment of acute pain and fever has not been studied in paediatric patients < 2 years of age

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

4. Hepatic impairment

Patients with Hepatic Impairment Acetaminophen is contraindicated in patients with severe hepatic impairment or severe active liver disease and should be used with caution in patients with hepatic impairment or active liver disease. A reduced total daily dose of acetaminophen may be warranted.

5. **Patients with Renal Impairment**

In cases of severe renal impairment (creatinine clearance ≤ 30 mL/min), longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients suffering from dizziness, vertigo, or other central nervous system disorders while taking NSAIDs should refrain from driving or handling dangerous machinery.

4.8 UNDESIRABLE EFFECTS

Adverse Effects of Aceclofenac:

1. **Gastrointestinal**

Most commonly observed adverse events are gastrointestinal. 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.

2. **Vascular and cardiac disorders**

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. Use of some NSAIDs particularly at high doses and in long term treatment, may be associated with an increased risk of arterial thrombotic events

3. **Blood and the lymphatic system disorders**

Aplastic anaemia

4. **Psychiatric disorders**

Hallucination, Confusional state

5. **Nervous System disorders**

Optic neuritis, somnolence

6. **Ear and labyrinth disorders**

Tinnitus

7. **Respiratory, thoracic and mediastinal disorders**

Aggravated asthma

8. **Skin and subcutaneous tissue disorders**

Toxic epidermal necrolysis, Erythema multiforme, Exfoliative dermatitis, photosensitivity reaction

9. Renal and urinary disorders

Interstitial nephritis

10. General disorders and administration site conditions

Malaise

Adverse Effects of Paracetamol:
SAFETY UPDATE: Fixed Drug Eruption(FDE) associated with Paracetamol

Reports of adverse reactions with paracetamol are rare. Nausea, allergic reactions, skin rashes, acute renal tubular necrosis. Potentially fatal: very rare, blood dyscrasias (e.g. Thrombocytopenia, leucopenia, neutropenia, agranulocytosis); liver damage

4.9 OVERDOSE
Overdosage may cause nausea, vomiting, pain abdomen, dizziness, somnolence, headache, sweating, pancreatitis, hepatic failure and acute renal failure.
Treatment, includes gastric lavage, activated charcoal and other symptomatic measures as per medical advice is needed.

Reported symptoms following overdose with other NSAIDs generally reflect the gastrointestinal, renal and CNS toxicities of NSAIDs. Patient must ingest a large quantity of Nimesulide, initiate symptomatic treatment including gastric lavage and restoration of water and electrolyte balance

Acute Overdose Management
Acute Paracetamol overdose is defined as an ingestion of a toxic amount of paracetamol occurring within a period of 8 hours or less.
In adults and adolescents, hepatic toxicity may occur following ingestion of greater than 7.5 to 10 g over a period of 8 hours or less

Gastric Decontamination/Prevention of Absorption
Gastric decontamination should be carried out according to standard treatment guidelines.

a) Activated charcoal should be given during the immediate postingestion period, especially in the case of a mixed drug overdose
b) Syrup of ipecac given to children during the prehospital phase may reduce subsequent plasma levels of paracetamol

Administration of Antidote
Based on clinical experience, if a patient presents soon after the overdose, treatment with acetylcysteine may be withheld until Paracetamol assay results are available, provided that initiation of treatment is not delayed beyond 8 hours following the overdose ingestion.
In adults and adolescents, immediately administer acetylcysteine orally or with a nasogastric tube if 8 hours or more have elapsed from the reported time of ingestion of an paracetamol overdose, regardless of the quantity of paracetamol reported to have been ingested. Do not await results of assays for Paracetamol level before initiating acetylcysteine.
The following procedures are recommended:

a) Administer the oral loading dose of acetylcysteine, 140 mg/kg of body weight.
b) Four hours after the loading dose, administer the first of 17 oral maintenance doses, 70 mg/kg of body weight. The oral maintenance dose is then repeated at 4-hour intervals for a total of 17 maintenance doses. If liver enzymes continue to be elevated, acetylcysteine may be continued beyond the full course of therapy until liver enzymes are decreasing and prothrombin time is returning to normal
c) If the patient vomits the loading dose or any maintenance dose within 1 hour of administration, repeat the dose.
d) For patients who are persistently unable to retain orally administered acetylcysteine, some poison control centers recommend aggressive antiemetic therapy or intravenous administration of acetylcysteine.

Laboratory test
In symptomatic patients or patients with increased plasma paracetamol levels, obtain aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels.
Bilirubin, prothrombin time or international normalized ratio (INR), creatinine, blood urea nitrogen (BUN), blood glucose, electrolyte, and pH levels may be useful, especially in cases showing evidence of significant toxicity.
Repeat the AST (or ALT) level daily during therapy if the plasma Paracetamol level is in the potentially toxic range. If AST or ALT levels are abnormal, then bilirubin, prothrombin time or INR, creatinine, BUN, blood glucose, electrolyte, and pH levels also should be obtained.

Management of overdosage in Pregnant Women
Acetylcysteine should not be withheld from pregnant women who have ingested Paracetamol overdose.

Management of overdosage in Patients Presenting 24 Hours or More Postingestion
Acetylcysteine may have a role in the management of patients who present more than 24 hours after paracetamol overdose.
Evidence suggests that acetylcysteine treatment may improve survival in patients presenting late and may be appropriate almost any time after overdose ingestion.

Management of overdosage in *Chronic Alcohol Users*
Chronic heavy alcohol users may be at an increased risk of hepatic toxicity from excessive paracetamol use
In these cases, a full course of acetylcysteine treatment should be administered

Management of overdosage in *Chronic (Repeated) Overdose*
Chronic overdose is defined as an ingestion of toxic amounts of Paracetamol taken for a period longer than 8 hours.
Acetylcysteine treatment should be considered in patients with a history of chronic overdose, especially when signs and symptoms are consistent with Paracetamol toxicity.
Paracetamol overdosage summary
When paracetamol overdose is a possibility, obtain a plasma paracetamol level and initiate antidotal therapy.
When the antidote, acetylcysteine, is administered using current recommendations, morbidity is significantly reduced and mortality virtually eliminated.

The prognosis for patients with parcetamol overdose is excellent, provided treatment is given expeditiously and appropriately.

5. PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION

Aceclofenac

Aceclofenac is a phenylacetic acid derivative nonsteroidal anti-inflammatory drug (NSAID) with marked anti-inflammatory and analgesic properties. It is a potent inhibitor of cyclooxygenase (COX),a key enzyme in the synthesis of prostaglandins and thromboxanes with selectivity for the COX-2 over COX-1 isoform.

Aceclofenac inhibits inflammatory mediators such as reactive oxygen species and IL-1beta, IL-6 and tumour necrosis factor-alpha.

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 is a weak inhibitor of the cyclooxygenase isoforms 1 or 2 (COX-1, COX-2) but more potent on COX-3.

Analgesic Action: The central analgesic action of paracetamol resembles that of aspirin. It produces analgesia by raising the pain threshold.

Although the exact site and mechanism of analgesic action is not clearly defined, acetaminophen appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.
Antipyretic Effect: The antipyretic effect of paracetamol is attributed to its ability to inhibit COX in the brain where the peroxide tone is low. Recent evidence suggests inhibition of COX-3 (believed to be a splice variant product of the COX-1 gene) and could represent a primary central mechanism by which paracetamol decreases pain and, possibly, fever.
Acetaminophen has been shown to inhibit the action of endogenous pyrogens on the heat-regulating centers in the brain by blocking the formation and release of prostaglandins in the central nervous system.

5.2 PHARMACODYNAMIC PROPERTIES

Aceclofenac reduced PGE2 in the synovial fluid ($p<0.05$ vs control), and protein expression ($p<0.05$ vs control) at the synovial membrane.
In clinical trials in patients with osteoarthritis patients scheduled for knee replacement surgery, 3-months' treatment with aceclofenac decreased IL-1β-induced release of PGE2 and decreased the synthesis of COX-2 and microsomal prostaglandin E synthase (mPGES)-1 in the cartilage and chondrocytes. In addition, aceclofenac reduced IL-1β-induced expression of TNFα and IL-1β in cultured OA chondrocytes. Aceclofenac also reduced lymphocyte adhesion in *in vitro* studies and increased glycosaminoglycan production in cartilage from OA patients.

Aceclofenac is effective in reducing pain and symptom severity, reduces joint tenderness, swelling, and erythema and improves the functional capacity in adults with osteoarthritis.

Paracetamol has analgesic and antipyretic effects. The combination of nonsteroidal anti-inflammatory drugs and paracetamol is more effective than paracetamol alone

5.3 PHARMACOKINETIC PROPERTIES

Parameters	Aceclofenac	Paracetamol
Absorption	Rapidly and completely absorbed as unchanged drug, peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion.	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. Effect after oral dose lasts for 3-5 hours
Distribution	Volume of distribution is approximately 25 L, Aceclofenac is highly protein bound >99%	Relatively uniformly distributed throughout most body fluids
Metabolism	Circulates mainly as unchanged drug. 4'-Hydroxyaceclofenac is the main metabolite detected in plasma	Metabolized predominantly in liver
Excretion	Approximately two-thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites	Excreted in the urine mainly as glucuronide and sulfate conjugate. Less than 5% is excreted unchanged.
Half-Life	Mean plasma elimination half-life is around 4 hours	The plasma half-life ($t_{1/2}$) 2-3 hours

6. NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Aceclofenac: In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy,

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). Acetaminophen has been reported to be clastogenic when administered a dose of 1,500 mg/kg/day to the rat model (3.6 times the MHDD, based on a body surface area comparison).

Oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights,

reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment

The subchronic toxicity of aceclofenac was studied in Wistar rats at doses ranging from 5 to 20 mg/kg Physiological , haematological and biochemical parameters were not found to be changed significantly .

7. DESCRIPTION

Nicoace Plus is supplied for oral administration, as film coated tablet of Aceclofenac and Paracetamol. Each film coated tablet of Nicoace Plus contains Aceclofenac 100 mg and Paracetamol 325 mg.

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES

Not applicable

8.2 SHELF-LIFE

Refer pack

8.3 PACKAGING INFORMATION

Refer pack

8.4 STORAGE AND HANDLING INSTRUCTIONS

Refer pack

9. PATIENT COUNSELING INFORMATION

Paracetamol must be taken as per the instructions of the doctor. Avoid overuse or use for long time as paracetamol may damage the liver.

Aceclofenac is an NSAID can causes gastrointestinal adverse effects. The patient must be advised to inform the doctor if he has had a bleeding peptic ulcer currently or in the recent past. Aceclofenac and all NSAIDs can cause changes in blood pressure in a hypertensive patient. The patient must be informed about the need to monitor BP. Since the use of NSAIDs may result in deterioration of renal function, patients with mild renal or cardiac impairment and the elderly should be receive this drug formulation under supervision.

The patients must be informed that cases of liver injury have been reported with the use of acetaminophen at doses that exceed the recommended maximum daily limit. Concomitant use of different pain medications that contain paracetamol is not advisable.

The patient must be advised to avoid taking NSAIDs:

- if he/ she has had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, the patient must tell his doctor about all his/ her medical conditions such as :

- liver or kidney problems
- high blood pressure
- asthma

If the patient is pregnant or plans to become pregnant, she must be advised to talk to her doctor if she is considering taking NSAIDs during pregnancy.

The patient must be advised to avoid taking NSAIDs after 29 weeks of pregnancy if she is breastfeeding or plans to breast feed.

The patient must be advised to tell the doctor about all of the medicines he/ she is taking , including prescription or over-the-counter medicines, vitamins, or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Advise the patient to avoid taking any new medicine without talking to the doctor first.

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

MARKETED BY
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, Maharashtra, India.
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11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
Refer Pack for Permission/License details

12. DATE OF REVISION
Version 2.0, dated 13/08/2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com