

Size: 240 (L) x 350 (H) mm
Folding size: 30 x 60 mm
Carton size: 85 x 85 x 60 mm

Front
240 mm



ACECLOFENAC + PARACETAMOL

DOLOWIN PLUS

100 mg / 500 mg Tablet

NON-STEROIDAL ANTI-INFLAMMATORY DRUG /
ANALGESIC / ANTIPYRETIC

PRODUCT NAME
DOLOWIN PLUS

DOSAGE FORM AND STRENGTH:
Tablets 100 & 500 mg

PHARMACOLOGIC CATEGORY:
Antipyretics, Anti-inflammatory and Antirheumatic Products, Non Steroids

PRODUCT DESCRIPTION
White oblong shaped film-coated tablets with a breakline on one surface.

FORMULATION/COMPOSITION:

Each film-coated tablet contains:
Aceclofenac BP100 mg
Paracetamol BP500 mg

PHARMACODYNAMICS/PHARMACOKINETICS:

Pharmacodynamics:

Aceclofenac relieves pain and inflammation through a variety of mechanisms and in addition exerts stimulatory effects on cartilage matrix synthesis.

Anti-inflammatory activity: The anti-inflammatory effects of Aceclofenac have been shown in both acute and chronic inflammation. It inhibits various mediators of pain and inflammation including:

- PGE2 via cyclo-oxygenase inhibition (COX-1 & COX-2) after intracellular metabolism to 4' hydroxy-Aceclofenac and diclofenac in human rheumatoid synovial cells and other inflammatory cells.
- IL-1 β, IL-6 and tumor necrosis factor in human osteoarthritis synovial cells and human articular chondrocytes.
- Reactive oxygen species (which plays a role in joint damage) has also been observed in patients with osteoarthritis of knee.
- 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 glycosaminoglycans

Synthesis in human osteoarthritis cartilage by inhibition of IL-1 β

And suppresses cartilage degeneration by inhibiting IL-1 β mediated promatrix metalloproteinase production and proteoglycan release.

Paracetamol is a clinically proven analgesic and antipyretic agent with 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.

Pharmacokinetics:

Absorption

Aceclofenac: Rapidly absorbed; almost 100% bioavailability; peak plasma levels reached about 1.25-3 hours after oral admin.

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion.

Distribution

Aceclofenac: >99.7% bound to plasma proteins; distributes into synovial fluid.

Paracetamol: Distributes throughout most fluids of the body.

Metabolism

Aceclofenac: Probably metabolised by CYP2C9; average plasma elimination half-life: 4-4.3 hours.

Paracetamol: Mainly metabolised hepatically; plasma elimination half-life: 1-4 hours.

Excretion

Aceclofenac: About two-thirds of the administered dose is removed in the urine, mainly as conjugated hydroxymetabolites.

Paracetamol: Most metabolites are removed in the urine within 24 hours.

INDICATIONS:

- Acute musculoskeletal painful conditions in adults
- Low back pain
- Acute flares of RA & OA
- Painful and inflammatory ENT conditions (Pharyngitis & tonsillitis)
- Post-operative pain
- Gynecological pain e.g. Dysmenorrhoeal
- Dental pain
- Fractures

DOSAGE AND MODEL ROUTE OF ADMINISTRATION:

Oral

Pain and inflammation

Adult: Each tablet contains Aceclofenac 100 mg and paracetamol 500 mg: 1 tablet in the morning and 1 tablet in the evening. Max: 2 tablets/day

CONTRAINDICATIONS & PRECAUTION(S), WARNING(S)

Dolowin Plus: is contraindicated in the following situations:

- Patients sensitive to Aceclofenac, Paracetamol or to any of the excipients of the product
- Patients in whom aspirin or other NSAIDs precipitate attacks of Bronchospasm, acute rhinitis or urticaria or patients hypersensitive to these drugs
- Patients with active or suspected peptic ulcer or gastrointestinal bleeding or bleeding disorders
- Patients with severe heart failure, hypertension, hepatic or renal insufficiency
- Last trimester of pregnancy

PRECAUTIONS & WARNINGS:

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

The use of Aceclofenac with concomitant NSAIDs including cyclo-oxygenase- 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 Tablets.

Hepatic:

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Aceclofenac Tablets should be discontinued. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms.

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

Hypersensitivity reactions:

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

Hematological:

Aceclofenac Tablets 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

Care is advised in the administration of Paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.

Contains Paracetamol

Do not take anything else containing Paracetamol while taking this medicine.

Talk to your doctor at once if you take too much of this medicine, even if you feel well. This is because too much Paracetamol can cause delayed, serious liver damage.

Patients should be advised that Paracetamol may cause severe skin reactions. If a skin reaction such as skin reddening, blisters, or rash occurs, they should stop use and seek medical assistance right away.

PREGNANCY AND LACTATION:

Aceclofenac

Pregnancy:

There is no information on the use of aceclofenac during pregnancy. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation or gastoschisis after use of prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, aceclofenac should not be given unless clearly necessary. If aceclofenac is used by a woman 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-hydroamnios; the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

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

Lactation:

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

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.

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.

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.

INTERACTIONS:

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

Anti-hypertensive: Reduced anti-hypertensive effect.

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

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

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate. 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.

Ciclosporin: Increased risk of nephrotoxicity.

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.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with Zidovudine. There is evidence of an increased risk of haemarthrosis 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

350 mm

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Antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycemic effects. Thus with Aceclofenac Tablets, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

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.

ADVERSE 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, angioedema 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 and epidemiological data consistently point towards an increased risk of general arterial thrombotic events (for example myocardial infarction or stroke, particularly at high doses or in long treatment). Epidemiological data has also found an increased risk of acute coronary syndrome and myocardial infarction associated with the use of aceclofenac. Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment

Other adverse reactions reported less commonly include:

Renal: interstitial nephritis.

Neurological and special senses: optic neuritis, reports of aseptic meningitis (especially in patients with existing auto immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, confusion, hallucinations, malaise and drowsiness.

Haematological: agranulocytosis, aplastic anaemia .

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

If serious adverse reactions occur, Aceclofenac should be withdrawn.

The following is a table of adverse reactions reported during clinical studies and after authorization, grouped by System-Organ Class and estimated frequencies. Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$)

MedDRA SOC	Common 1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare < ≥1/10,000 to <1/1,000	Very rare/ <1/10,000
Blood and lymphatic system disorders			Anaemia	Bone Marrow depression Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Metabolism and nutrition disorders				Hyperkalemia
Psychiatric disorders				Depression Abnormal dreams Insomnia
Nervous system disorders	Dizziness			Paraesthesia Tremor Somnolence Headache Dysgeusia (abnormal taste)
Eye disorders			Visual disturbance	
Ear and labyrinth disorders				Vertigo Tinnitus
Cardiac disorders			Cardiac failure	Palpitations
Vascular disorders			Hypertension	Flushing Hot flush Vasculitis
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm Stridor
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulceration	Melaena Gastrointestinal haemorrhage Gastrointestinal ulceration	Stomatitis Intestinal perforation Exacerbation of Crohn's disease and Colitis Ulcerative Hematemesis 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: Nausea, allergic reactions, skin rashes, acute renal tubular necrosis. Aceclofenac: Diarrhoea, headache, vertigo, dizzies nervousness, tinnitus, depression, drowsiness, insomnia; fever, angioedema, Bronchospasm, rashes; blood dyscrasias. Potentially Fatal: Paracetamol: Very rare, blood dyscrasias (e.g. thrombocytopenia, leucopenia, neutropenia, agranulocytosis); liver damage. Aceclofenac: Severe GI bleeding; nephrotoxicity.

OVERDOSAGE AND TREATMENT:

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 life-threatening 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, gastrointestinal irritation, and respiratory depression.

Paracetamol

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

Risk Factors

If the patient

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

Or

b) Regularly consumes ethanol in excess of recommended amounts.

Or

c) 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, hemorrhage, hypoglycemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of Paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

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-acetyl cysteine may be used up to 24 hours after ingestion of Paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion.

If required the patient should be given intravenous-N-acetyl cysteine, 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 24 hours from ingestion should be discussed with the NPIS or a liver unit.

STORAGE CONDITION:

Store at temperatures not exceeding 30°C

DOSAGE FORMS AND PACKAGING AVAILABLE:

Tablets
Alu/PVC Blister Pack of 10's (Box of 100's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):

Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:

Marketing Authorization Holder

Brown & Burk Philippines Inc
U-501, 5/F, SEDCCO 1 Bldg., 120 Rada cor., Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:

MICRO LABS LIMITED-Unit III,
63/3&4, Thiruvandar Koil,
Puducherry-605 102, India.

CAUTION STATEMENT:

FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATEMENT:

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of Adverse Drug Reaction.

REGISTRATION NUMBER:

DR-XY43902

DATE OF FIRST AUTHORIZATION:

21 November 2014

DATE OF REVISION OF PACKAGE INSERT:

Oct. 2019

EXG-ML05I-0202/A

350 mm

MICRO LABS LIMITED, BANGALORE, INDIA

1	Product Name	Dolowin Plus	Colours Used ■ BLACK			
2	Strength	100 mg and 500 mg				
3	Component	Leaflet				
4	Category	Export - Philippines				
5	Dimension	240 x 350 mm				
6	Artwork Code	EXG-ML05I-0202/A				
7	Pharma Code	N/A				
8	Reason for Change	Size and New Regulation text				
Prepared by (DTP)		Checked by (PD)	Approved by			
Sign	Kantharaju L.		Head CQA	Head Production (Site)	Head QC (Site)	Head QA (Site)
Date	02-02-2022					