Front Side

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ACECLOFENAC

DOLOWIN ™

100 mg Film-Coated Tablet
ANTI-INFLAMMATORY AND ANTI-RHEUMATIC
(ACETIC ACID DERIVATIVES)

PRODUCT DESCRIPTION:
White, circular, biconvex film – coated tablets, plain on both sides.

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Aceclofenac BP ……..... 100 mg

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics:
Aceclofenac is an NSAID known to exhibit multifactor mechanism of action. Aceclofenac was developed in order to provide a highly effective pain relieving therapy with a reduced side effect profile.

- Aceclofenac directly blocks PGE 2 secretion at the site of inflammation by inhibiting IL-Beta & TNF in the inflammatory cells (Intracellular Action).Aceclofenac has been demonstrated to inhibit cyclo-oxygenase (COX) activity and to suppress the PGE 2 production by inflammatory cells, which are likely to be a primary source of PGE 2 . Inflammatory cells release IL-1 and TNF, which produce PGE 2 by induction of COX-2. Aceclofenac and 4`-hydroxyaceclofenac penetrate the inflammatory cells like polymorphonuclears, monocytes and rheumatoid synovial cells and get hydrolyzed to the active metabolites diclofenac and 4`-hydroxydiclofenac which inhibit IL-1 and TNF released by the inflammatory cells and therefore suppress production of PGE 2 at the site of inflammation.
- Aceclofenac stimulates the synthesis of the extracellular matrix of the Human Articular Cartilages. Aceclofenac blocks degeneration and stimulates synthesis of extracellular matrix of cartilages by inhibiting the action of different cytokines. Aceclofenac and the metabolites inhibit IL-6 production by human chondrocytes. This leads to inhibition of increase of inflammatory cells in synovial tissue, inhibition of IL-1 amplification, inhibition of increased MMP synthesis and thus ensuring proteoglycan production. Aceclofenac also inhibits IL-1 and TNF production by human chondrocytes, inflammatory cells and synovial cells and therefore blocks suppression of GAG and collagen synthesis and stimulates growth factor mediated synthesis of GAG and collagen. 4`-hydroxyaceclofenac, a metabolite of Aceclofenac inhibits pro MMP1 and pro MMP3 produced by synovial cells (Rheumatoid Synovial Cells) in serum and in synovial fluid and thus inhibits progressive joint destruction by MMPs.

Aceclofenac inhibits Neutrophils Adhesion & Accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of Neutrophils.

Pharmacokinetics:
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'- hydroxyacelofenac 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.

INDICATIONS:
It is used in the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

DOSAGE AND MODE ROUTE OF ADMINISTRATION:
Aceclofenac film-coated tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid.
To be taken preferably with or after food. When Aceclofenac was administered to fasting and fed healthy volunteers only the rate and not the extent of Aceclofenac absorption was affected.
Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.
Adults
The recommended dose is 200 mg daily, taken as two separate 100 mg doses, one tablet in the morning and one in the evening.
Paediatric population
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.
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.
The pharmacokinetics of Aceclofenac are not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency.
Renal insufficiency
There is no evidence that the dosage of Aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised.
Hepatic insufficiency
There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used.

CONTRAINDICATIONS &PRECAUTION(S), WARNING(S)
Hypersensitivity to Aceclofenac or to any of the 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 (e.g. Asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
Severe heart failure, hepatic failure and renal failure
History of gastrointestinal bleeding or perforation, related to previous NSAIDS therapy.
Aceclofenac should not be prescribed during pregnancy, especially during the last trimester of pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used

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.

PREGNANCY AND LACTATION:
Pregnancy: 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

PHARMACODE READING DIRECTION

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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.
Lactation: 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 Tablets should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

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 (+) haemaophiliacs 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 hypoglycemic and hyperglycemic effects. Thus with Aceclofenac Tablets, consideration should be given to adjustment of the dosage of hypoglycemic agents.
Other NSAIDs: Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

ADVERSE EFFECTS:
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, hematemesis, 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 multiform).
Cardiovascular:
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).
Other adverse reactions reported less commonly include:
Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephritic 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 erythematous, 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.
Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia and haemolytic anemia
Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity

OVERDOSAGE AND TREATMENT:
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 and 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 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 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.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Aceclofenac Tablets 100 mg (Dolowin) are Packed in Alu/Alu Blister Pack of 10's(Box of 30)

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:
Manufactured by :
MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur-635 126 (T.N.), 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 sigh of Adverse Drug Reaction.

REGISTRATION NUMBER:
DR No. : XY41396

DATE OF FIRST AUTHORIZATION:
11 January 2018

DATE OF REVISION OF PACKAGE INSERT:
Feb. 2019

EXG-ML01I-1879

Paper 35 to 50 gsm

14 (L) x 8 (H) mm

PHARMACODE READING DIRECTION

770

Size : 170 (L) x 280 (H) mm
Drg. No.: W0990006889Z-000
Folding size: 35 x 170 mm
Carton size: 53 x 25 x 130 mm

MICRO LABS LIMITED, BANGALORE, INDIA			
1	Product Name	Dolowin	Colours Used
2	Strength	100 mg	BLACK
3	Component	Leaflet	
4	Category	Export - Philippines	
5	Dimension	170 (L) x 280 (H) mm	
6	Artwork Code	EXG-ML01I-1879	
7	Pharma Code	770	
8	Reason for Change	New Artwork	Colours not for Printing Keylines

	Prepared by (DTP)	Checked by (PD)	Approved by			
			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kantharaju L.					
Date	03-10-2023					