SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

1.1 Product Name:

Aceclofenac & Paracetamol Tablets

Dolowin Plus

1.2 Strength:

100/500 mg

2. Quality and Quantitative Composition

Each film-coated tablet contains:

Aceclofenac BP ……..100 mg

Paracetamol BP …….…….500mg

3. Pharmaceutical Form

Film coated Tablets

4. Clinical Particulars

4.1 Therapeutic 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. Dysmenorrheal
- Dental pain
- Fractures

4.2 Posology and method 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.

4.3 Contraindications:

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

4.3 Special warning and precautions:

Aceclofenac

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 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 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.
Use of Aceclofenac Tablets 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.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial

thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for Aceclofenac.

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, hyperlipidemia, 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 hematological 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 hemorrhage 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.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
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 erythematous (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 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.

4.4 Interaction with other medicinal products and other forms of 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.

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 hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) hemophiliacs 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.

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.

4.5 Pregnancy and lactation:

Aceclofenac

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 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.

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.

4.6 Undesirable 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 dermatosis (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.

Hematological:

Thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia and haemolytic anemia

Dermatological:

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

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, leucopoenia, neutropenia, agranulocytosis); liver damage. Aceclofenac: Severe GI bleeding; nephrotoxicity.

4.7 Overdose:

Aceclofenac

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally 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 NSAIDs essentially consists of supportive and symptomatic measures.

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.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

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 (be lived to be splice variant product of the COX-1 gene) could represent a primary central mechanism by which Paracetamol decreases pain and possibly fever.

5.2 Pharmacokinetic Properties

Absorption

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

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.

5.3 Preclinical safety data

Aceclofenac

The results from preclinical studies conducted with Aceclofenac are consistent with those expected for NSAIDs. The principal target organ was the gastro-intestinal tract.

No unexpected findings were recorded.

Aceclofenac was not considered to have any mutagenic activity in three *in vitro* studies and an *in vivo* study in the mouse.

Aceclofenac was not found to be carcinogenic in either the mouse or rat.

6. Pharmaceutical Particulars

6.1 List of excipients:

MAIZE STARCH BP
COLLOIDAL ANHYDROUS SILICA BP
CROSCARMELLOSE SODIUM BP
METHYL HYDROXY BENZOATE BP
PROPYL HYDROXY BENZOA TE BP
POVIDONE BP (K 30)
MICROCRYSTALLINE CELLULOSE BP
MAGNESIUM STEARA TE BP
HYPROMELLOSE BP
TITANIUM DIOXIDE BP
TALC BP
POLYSORBA TE-80 BP

6.2 Incompatibilities:

None known

6.3 Shelf life:

36 months from the date of manufacturing.

6.4 Special precautions for storage:

Store at temperatures not above 30°C

6.5 Nature and contents of container:

Blister Pack of 10 Tablets

7. Marketing Authorization Holder:

MICRO LABS LIMITED

92, SIPCOT,

HOSUR-635 126

INDIA

8. Marketing Authorization Numbers

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9. Date of first authorization

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10. Date of revision of the text

July 2019