SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

1.1 Product Name

Dolowin SR 200

1.2 Strength:

200 mg

2. Quality and Quantitative Composition

Each film coated sustain release tablets contains: Aceclofenac BP Tablets …….200 mg

3. Pharmaceutical Form

Film Coated Tablets

4. Clinical Particulars

4.1 Therapeutic indications:

It is indicated for treatment of Osteoarthritis, Rheumatoid arthritis, Spondylitis (the drug of choice), Dental pain, Post operative pain and Dysmenorrheal.

4.2 Posology and method of administration:

The usual dose of Aceclofenac 200 mg sustained release is once daily given by mouth. 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. There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment.

4.3 Contraindications:

It should not be administered to patients hypersensitive to Aceclofenac or other NSAIDs, or patients with a history of aspirin or NSAID related allergic or anaphylactic reactions or with peptic ulcers or GI bleeding, moderate or severe renal impairment.

4.4 Special warning and precautions:

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.

4.5 Interaction with other medicinal products and other forms of interactions:

Drug interactions associated with Aceclofenac are similar to those observed with other NSAIDs. Aceclofenac may increase plasma concentrations of lithium, digoxin and Methotrexate, increase the activity of anticoagulants, inhibit the activity of diuretics, enhance cyclosporin nephrotoxicity and precipitate convulsions when co-administered with quinolone antibiotics. When concomitant administration with potassium sparing diuretics is employed, serum potassium should be monitored. Furthermore, hypo or hyperglycemias may result from the concomitant administration of Aceclofenac and antidiabetic drugs, although this is rare. The co-administration of Aceclofenac with other NSAIDs or corticosteroids may result in increased frequency of side effects. Caution should be exercised if NSAIDs and Methotrexate are administered within 2-4 hours of each other, since NSAIDs may increase Methotrexate plasma levels, resulting in increased toxicity.

4.6 Pregnancy and lactation:

Pregnancy

Pregnancy D There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans but potential benefits may warrant use of the drug in pregnant women despite potential risks

Lactation

Lactation L4 There is positive evidence of risk to a breastfed infant or to breast milk production but the benefits of use in breastfeeding mothers may be acceptable despite the risk to the infant e.g. if the drug is needed in a life threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.

4.7 Undesirable effects:

The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are gastro-intestinal disorders, in particular dyspepsia, abdominal pain, nausea and diarrhea, and occasional occurrence of dizziness. Dermatological complaints including pruritus and rash and abnormal hepatic enzyme and serum creatinine levels have also been reported with the frequencies indicated in the following table. If serious adverse reactions occur, Aceclofenac should be withdrawn.

Undesirable effects associated with NSAIDs in general:

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, diarrhea, 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. *Vascular and cardiac disorders:* 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 rare or very rare class effects reported with NSAIDs in general are:

Blood and the lymphatic system disorders – Aplastic anaemia

Psychiatric disorders – Hallucination, Confusional state

Nervous system disorders – Optic neuritis, somnolence

Ear and labyrinth disorders – Tinnitus

Respiratory, thoracic and mediastinal disorders – Aggravated asthma

Skin and subcutaneous tissue disorder – Toxic epidermal necrolysis, Erythema multiform, Exfoliative dermatitis, and photosensitivity reaction. *Renal and urinary disorders* – Interstitial

nephritis

General disorders and administration site conditions – Malaise

Other rare or very rare class effects reported with NSAIDs in general are: *Blood and the lymphatic system disorders* – Aplastic anaemia

Psychiatric disorders – Hallucination, Confusional state

Nervous system disorders – Optic neuritis, somnolence

Ear and labyrinth disorders – Tinnitus

Respiratory, thoracic and mediastinal disorders – Aggravated asthma

Skin and subcutaneous tissue disorder – Toxic epidermal necrolysis, Erythema multiform, Exfoliative dermatitis, photosensitivity reaction. *Renal and urinary disorders* – Interstitial nephritis

General disorders and administration site conditions – Malaise

4.8 Overdose:

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.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

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.

5.2 Pharmacokinetic Properties

Absorption:

After oral administration, Aceclofenac is rapidly absorbed and the bioavailability is almost 100%. Peak plasma concentrations are reached approximately 1.25 to 3 hours following ingestion. T max is delayed with concomitant food intake whereas the degree of absorption is not influenced.

Distribution:

Aceclofenac is highly protein-bound (> 99.7%). Aceclofenac penetrates into the synovial fluid where the concentrations reach approximately 60% of those in plasma. The volume of distribution is approximately 30L.

Metabolism*:*

Aceclofenac is probably metabolized via CYP2C9 to the main metabolite 4-hydroxyaceclofenac. The mean plasma elimination half-life is 4-4.3 hours.

Excretion:

Approximately two-thirds of the administered dose is excreted via the urine, mainly as conjugated hydroxymetabolites. Only 1% of an oral single dose is excreted unchanged. A slower rate of elimination of Aceclofenac has been detected in patients with decreased liver function

after a single dose of Aceclofenac. In a multiple dose study using 100 mg once daily, there was no difference in the pharmacokinetic parameters between subjects with mild to moderate liver cirrhosis and normal subjects. In patients with mild to moderate renal impairment, no clinically significant differences in the pharmacokinetics were observed after a single dose.

6. Pharmaceutical Particulars

6.1 List of excipients:

CORE

Microcrystalline Cellulose, Magnesium stearate, Colloidal anhydrous silica, Hypromellose.

COAT

Isopropyl alcohol, Dichloromethane, Titanium Dioxide, Talc, Ponceau 4R (Color Lake),Polyethylene Glycol 6000

6.2 Incompatibilities:

None known

6.3 Shelf life:

36 months from the date of manufacturing.

6.4 Special precautions for storage:

Store below 30°C. Keep out from reach of children

6.5 Nature and contents of container:

Alu/Alu Blister pack of 3x10’s

7. Marketing Authorization Holder:

MICRO LABS LIMITED

27, Race course road

Bangalore-560001

8. Marketing Authorization Numbers

--

9. Date of first authorization

--

10. Date of revision of the text

April 2019