Summary of Product Characteristics

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ZIFLAM 200 SR (Aceclofenac Sustained Release Capsules 200 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:
Aceclofenac BP 200 mg
(In Sustained Release Form)

3. PHARMACEUTICAL FORM

Hard gelatin capsule
Maroon and white, Size "0", hard gelatin capsules containing white to off-white coated pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aceclofenac is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults.

4.2 Posology and method of administration

Posology:

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 one dose (every 24 hours). However, the dose and dose frequency of Aceclofenac can be modified under the supervision of physician or pharmacist.

Children: There are no clinical data on the use of Aceclofenac capsules 200 mg in children and therefore it is not recommended for use in children.

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 the 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.

Patients with renal impairment: 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.

Method of administration

Aceclofenac capsules are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid. To be taken preferably with or after food.

4.3 Contraindication

- Hypersensitivity to the active substances or to any of the excipients used in formulation.
- 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.
- Patients with active bleeding or bleeding diathesis.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

4.4 Special warnings and special precautions for use

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.

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 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 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 congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy. As the cardiovascular risks of aceclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically. Aceclofenac should also be administered with caution and under close medical surveillance to patients with a history of cerebrovascular bleeding.

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 haematological 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 haemorrhage 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 erythematosus (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 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can trigger serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of aceclofenac in case of varicella.

Impaired female 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.

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

Haematological: Aceclofenac may reversibly inhibit platelet aggregation.

Aceclofenac should be avoided in patients who have developed anaemia, agranulocytosis or thrombocytopenia secondary to NSAIDs or metamizol.

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 interaction

- *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-hypertensives:* Reduced anti-hypertensive effect. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ACE- inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

- *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 like digoxin:* NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels. The combination should be avoided unless frequent monitoring of glycoside levels can be performed.

- *Lithium:* The combination should be avoided unless frequent monitoring of lithium can be performed.

- *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.

- *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 therapy should be undertaken.

- *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.

- *Cyclosporin, Tacrolimus:* Administration of NSAID drugs together with cyclosporin or tacrolimus is thought to increase the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. During combination therapy it is therefore important to carefully monitor renal function.

- *Zidovudine:* Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses 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 antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects. Thus with Aceclofenac, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

- *Other NSAIDs:* Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

4.6 Pregnancy and lactation

Since there is no information on the safe use of Aceclofenac during pregnancy and lactation, the use of Aceclofenac should therefore be avoided in pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 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, 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, angiodema 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 increased risk of general arterial thrombotic events (myocardial infarction or stroke, particularly at high doses and in long treatment). Also, 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.

Hepatic: abnormal liver function, hepatitis and jaundice.

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, 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.

Undesirable effects are listed under headings of frequency, using the following categories: very common (≥1/10); 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), not known (cannot be estimated from the available data).

Common: Dizziness, Dyspepsia, Abdominal pain, Nausea, Diarrhoea, Hepatic enzyme increased

Uncommon: Flatulence, Gastritis, Constipation, Vomiting, Mouth ulceration, Pruritus, Rash, Dermatitis, Urticaria, Blood urea increased, Blood creatinine increased

Rare: Anaemia, Anaphylactic reaction (including shock), Hypersensitivity, Visual disturbance, Cardiac failure, Hypertension, Dyspnoea, Melaena, Gastrointestinal haemorrhage, Gastrointestinal ulceration, Angioedema

Very Rare: Granulocytopenia, Thrombocytopenia, Neutropenia, Haemolytic anaemia, Hyperkalemia, Depression, Abnormal dreams, Insomnia, Paraesthesia, Tremor, Somnolence, Headache, Dysgeusia (abnormal taste), Vertigo, Tinnitus, Palpitations, Flushing, Hot flush, Vasculitis, Bronchospasm, Stridor, Stomatitis, Intestinal perforation, Exacerbation of Crohn's disease and Colitis Ulcerative, Haematemesis, Pancreatitis, Hepatic injury (including hepatitis), Jaundice, Blood alkaline phosphatase increased, Purpura, Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis), Renal failure, Nephrotic syndrome, Oedema, Fatigue, Cramps in legs, Weight increase.

4.9 Overdose

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures.

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 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, gastro-intestinal irritation, and respiratory depression.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, nonsteroids, acetic acid derivatives and related substances
ATC Code: M01AB16.

Aceclofenac is non-steroidal agent with marked anti-inflammatory and analgesic properties. The mode of action of Aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme

cyclooxygenase, which is involved in the production of prostaglandins.

5.2 Pharmacokinetic Properties

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'-Hydroxyaceclofenac is the main metabolite detected in plasma. Approximately two-thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites.

Aceclofenac is partially metabolised to diclofenac.

No changes in the pharmacokinetics of Aceclofenac have been detected in the elderly.

5.3 Preclinical safety data

The results from preclinical studies conducted with aceclofenac are consistent with those expected for NSAIDs. The principal target organ was the gastrointestinal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Polysorbate 80
Mannitol
Hypromellose 5cps
Microcrystalline cellulose
Ethylcellulose
Dibutyl Phthalate
Methacrylic Acid
Copolymer (Type A)
Titanium dioxide
Purified talc
N.P Seeds
Isopropyl Alcohol
Dichloromethane
Empty Hard gelatin capsule

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C, protect from light and moisture.
Keep out of the reach of children.

6.5 Nature and content of container

Alu-Alu Cold forming blister pack of 10 capsules. Such 3 blister packed in carton**.**

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zim Laboratories Limited.
Sadoday Gyan (Ground Floor),
Opp. NADT, Nelson Square,
Nagpur – 440013
India.

8. MARKETING AUTHORISATION NUMBERS

04867/5969/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/12/2019

10. DATE OF REVISION OF THE TEXT

01/07/2023