National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Drug Product

Zerodol (Aceclofenac Tablets 100mg)

2. Qualitative and Quantitative Composition

Each film coated tablet contains:
Aceclofenac BP….100mg

3. Dosage form

Film coated Tablet
Reddish brown coloured, circular, biconvex, film coated tablets with breakline on one side and 'ZRD' embossed on other side.

4. Clinical characteristics

4.1. Therapeutic Indications

Symptomatic therapy of pain syndrome and inflammation in osteoarthritis and rheumatoid arthritis, ankylosing spondylitis and other diseases of the musculoskeletal system, accompanied by pain (example humeroscapular periarthritis or extraarticular rheumatism)
As analgesic in conditions involving pain (including pain in the lumbar, toothache and primary (functional) dysmenorrhea)

4.2 Usage forms and dosages

The usual dose of aceclofenac is 100mg given twice daily by mouth. One tablet in the morning and one in the evening.

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 and it is suggested that an initial daily dose of 100mg be used.

Aceclofenac tablets should be swallowed whole with a sufficient quantity of liquid. When aceclofenac was administered to fasting and fed healthy volunteers

only the rate and not the extent of aceclofenac absorption was affected and as such aceclofenac can be taken with food

4.3. Contra-indications

Aceclofenac 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 Warnings and Precautions for Use

WARNINGS

Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastrointestinal ulceration, with ulcerative colitis or with Crohn's disease, bleeding diathesis or haematological abnormalities.

Gastrointestinal bleeding or ulcerative perforation, haematemesis and melaena have in general more serious consequences in the elderly. They can occur at any time during treatment, with or without warning symptoms or previous history. In the rare instances, where gastrointestinal bleeding or ulceration occurs in patients receiving aceclofenac, the drug should be withdrawn.

Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

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

PRECAUTIONS

Aceclofenac should be given with caution to elderly patients with renal, hepatic or cardiovascular impairment and to those receiving other medication. The lowest effective dose should be used and renal function monitored regularly.
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.

Caution should also be exercised in patients with history of coagulation defects and history of liver dysfunction

Renal and hepatic function and blood counts should be monitored during long term treatment. Persistently elevated hepatic enzyme levels necessitate withdrawal of aceclofenac.

Aceclofenac may trigger attacks in patients with hepatic porphyria, and reversible inhibition of platelet aggregation may occur with the drug.

Refrain from driving or operating machinery if there is feeling of dizziness or sleepiness whilst taking aceclofenac. Do not perform any of these actions until the effects wear off.

Usage in pregnancy and lactation

The drug is not recommended in pregnant or breast feeding women.

Usage in pediatrics

There are no clinical data on the use of aceclofenac in children.

Usage in geriatrics

The pharmacokinetics of aceclofenac is not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency.

As with other non-steroidal anti-inflammatory drugs (NSAIDs), caution should be exercised in the treatment of elderly patients, who are generally more prone to adverse reactions, and who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

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 coadministered with quinolone antibiotics.

When concomitant administration with potassium sparing diuretics is employed, serum potassium should be monitored.

Furthermore, hypo or hyperglycaemia may result from the concomitant administration of aceclofenac and antidiabetic drugs, although this is rare. The coadministration of aceclofenac with other NSAIDs or corticosteroids may result in increased frequency of adverse events.

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

The drug is not recommended in pregnant or breast feeding women.

4.7. Effects on Ability to Drive and Use Machines

Patients who experience dizziness or other central nervous system disturbances While taking NSAIDs should refrain from driving or operating machinery.

4.8. Undesirable Effects

Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the Gastro-intestinal (GI) system.

Most common events include dyspepsia, and abdominal pain (>5% incidence). Dizziness, vertigo, pruritus, rash and dermatitis have been reported with aceclofenac, but the incidence of these events is low (<5%)
Fecal blood loss was noted in similar numbers of patients receiving aceclofenac or comparator drugs. Nausea, diarrhoea, flatulence, gastritis, constipation, vomiting and ulcerative stomatitis may also occur with aceclofenac (<5% incidence)

Increases in blood urea nitrogen and blood creatinine levels have also been reported with aceclofenac treatment (incidence <5%). As with other NSAIDs, aceclofenac can elevate circulating levels of hepatic enzymes.

Although the incidence of GI adverse events with aceclofenac was similar to those of comparator NSAIDs in individual clinical trials, withdrawal rates due to these events were significantly lower with aceclofenac than with ketoprofen and tenoxicam. Costs incurred as a result of adverse event management are lower with aceclofenac than with a range of comparator NSAIDs. Although statistical analyses were not consistently available, faecal bleeding and endoscopy studies in humans have indicated overall less GI bleeding and GI mucosal damage with aceclofenac than with naproxen or diclofenac.

The following adverse events (described as most frequent >5%, occasional < 5% or rare cases < 0.1%) were reported during all clinical trials:

Gastrointestinal disorders: Most frequent: dyspepsia (7.5%), abdominal pain (6.2%), Occasional: nausea (1.5%), diarrhoea (1.5%), flatulence (0.8%), gastritis (0.6%), constipation (0.5%), vomiting (0.5%), ulcerative stomatitis (0.1%). Rare cases: (all <0.1%) pancreatitis, melaena, stomatitis

Central and peripheral nervous system: Occasional: dizziness (1%), vertigo (0.3%). Rare cases: (all <0.1%), paraesthesia, tremor
Psychiatric: Rare cases: (all <0.1%) depression, abnormal dreaming, somnolence, insomnia

Skin and appendages: Occasional: pruritus (0.9%), rash (0.5%), dermatitis (0.2%). Rare cases: (all <0.1%) eczema
Liver and biliary: Occasional: hepatic enzymes increased (2.5%)
Metabolic: Occasional: BUN increased (0.4%), blood creatinine increased (0.3%). Rare cases (all <0.1%) alkaline phosphatase increased, hyperkalaemia

Cardiovascular: Rare cases: (all <0.1%) oedema (dependent), palpitation, leg cramps, flushing, purpura.

Respiratory: Rare cases: (all <0.1%) dyspnoea, stridor

Blood: Rare cases: (all <0.1%) anaemia, granulocytopenia, thrombocytopenia

Body as whole, general: Rare cases: (all <0.1%) headache, fatigue, face, oedema, hot flushes, allergic reaction, weight increase

Other: Rare cases: (all < 0.1%) abnormal vision, abnormal taste

4.9. Overdose

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

There are no human data available on the consequences of aceclofenac overdosage. The therapeutic measures to be taken are: absorption should be prevented, as soon as possible after overdosage by means of gastric lavage and treatment with activated charcoal; supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation, and respiratory depression, specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Aceclofenac has been shown to exert effects on a variety of mediators of inflammation. The drug inhibits synthesis of the inflammatory cytokines interleukin (IL)-1ß and tumour necrosis factor and inhibits prostaglandin E2 (PGE2) production. Effects on cell adhesion molecules from neutrophils have also been noted. In vitro data indicate inhibition of cyclo-oxygenase (COX)-1 and 2 by aceclofenac in whole blood assays, with selectivity for COX-2 being evident.

In contrast to some other NSAlDs, aceclofenac has shown stimulatory effects on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit IL-1ß activity. In vitro data indicate stimulation by the drug of synthesis of glycosaminoglycan in osteoarthritic cartilage. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyaceclofenac has chondroprotective properties attributable to suppression of IL-1ß mediated promatrix metalloproleinase production and proteoglycan release.

In patients with osteoarthritis of the knee, aceclofenac decreases pain, reduces disease severity and improves the functional capacity of the knee. It reduces joint

inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain intensity are reduced and spinal mobility improved, by aceclofenac in patients with ankylosing spondylitis.

5.2. Pharmacokinetic Properties

Aceclofenac is rapidly and completely absorbed after oral administration. Peak plasma concentrations are reached 1 to 3 hours after an oral dose. The drug is highly protein bound (>99%). The presence of food does not alter the extent of absorption of aceclofenac but the absorption rate is reduced. The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in patients with knee pain and synovial fluid effusion.

Aceclofenac is metabolised to a major metabolite, 4'-hyciroxyaceclofenac and to a number of other metabolites including 5-hydroxyaceclofenac, 4'-hydroxydiclofenac, diclofenac and 5-hydraxydiclofenac. These other metabolites account for the fate of approximately 20% of each dose of aceclofenac Renal excretion is the main route of elimination of aceclofenac with 70 to 80% of an administered dose found in the urine, mainly as the glucuronides ot aceclofenac and its metabolites. of each dose of aceclofenac, 20% is excreted in the faeces. The plasma elimination half life of the drug is approximately 4 hours.

5.3. Preclinical Safety Data

Carcinogenic studies in the mouse (systemic exposure to aceclofenac unknown and in the rat (metabolism to diclofenac) did not show any carcinogenic effects and aceclofenac was negative in genotoxicity tests.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (1 0 mg/kg/day) resulted in a series of morphological changes in some foetuses.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipient(s)

Microcrystalline Cellulose BP/EP, Croscarmellose Sodium BP/EP, Sodium Starch Glycollate BP/EP, Colloidal Silicon Dioxide (Anhydrous) BP/EP, Sodium Lauryl Sulphate BP/EP, Ferric Oxide Red USP-NF, Polyoxyl-40 Hydrogenated Castor Oil USP-NF, HPMC BP/EP, Isopropyl Alcohol BP/EP, Methylene Chloride EP, Crosspovidone BP/EP, Stearic acid BP/EP, Titanium Dioxide BP/EP, Purified Talc BP/EP, Dibutyl phthalate BP/EP.

6.2 Incompatibilities

Not applicable

6.3. Shelf Life

36 months

6.4. Special Precautions for Storage

Store below 30°C in a dry place.

6.5. Nature and Contents of Container

Blister strips of 10 tablets. 1 such strip packed in a printed showbox along with a leaflet.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Ipca Pharma Nig Ltd.
No, 3, llupeju Bye Pass,
(Olajire House) llupeju Lagos,
ipcaharma@yahoo.com

8. DRUG PRODUCT MANUFACTURER

Ipca Laboratories Ltd.
Sejavta, Ratlam 457 002
Regd. Off.: 48, Kandivli Ind. Estate,
Mumbai 400 067

9. NAFDAC REGISTRATION NUMBER :

A4-2257