1. NAME OF THE MEDICINAL PRODUCT

Zerodol-CR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zerodol-CR (Aceclofenac Controlled Release Tablets 200 mg)

Each film coated controlled release tablet contains:

Aceclofenac BP.....200 mg

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Aceclofenac controlled release tablets are indicated for the relief of pain and inflammation associated with rheumatoid arthritis, osteoarthritis or ankylosing spondylitis.

4.2 Posology and Method of Administration

The usual dosage of Aceclofenac controlled release tablets is one tablet once daily to be given by mouth.

As with other NSAIDs, caution should be exercised in patients with renal impairment.

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 (conventional Aceclofenac tablets) be used.

Aceclofenac controlled release tablets should be swallowed whole with a sufficient quantity of liquid.

4.2. 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.

4.3. 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instances, where gastrointestinal bleeding or ulceration occurs in patients receiving Aceclofenac, the drug should be withdrawn.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. Renal function should be 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 paediatrics

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

Usage in geriatrics

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.

Drug 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 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. Usage in pregnancy and lactation

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

4.7 ADVERSE DRUG REACTIONS

Aceclofenac is well tolerated, with most adverse events being minor and reversible and affecting mainly the GI system.

Most common events include dyspepsia, and abdominal pain. Dizziness, vertigo, pruritus, rash and dermatitis have been reported with Aceclofenac, but the incidence of these events is low.

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 with conventional Aceclofenac 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

4.8 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. 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.

Aceclofenac has been shown to exert effects on a variety of mediators of inflammation. The drug inhibits synthesis of the inflammatory cytokines

interleukin (IL)-1 and tumour necrosis factor and inhibits prostaglandin E2 (PGE2) production.

In contrast to some other NSAIDs, Aceclofenac has shown stimulatory effects on cartilage matrix synthesis, that may be linked to the ability of the drug to inhibit IL-1β activity.

5.2. Pharmacokinetic Properties

Aceclofenac is rapidly and completely absorbed after oral administration.

Release of Aceclofenac from the controlled release tablets is Zero order, which is obtained through special matrix embedded monolithic device with release retardant and bio-degradable polymer in combination and with non functional coating.

The drug is highly protein bound (>99%). 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'-hydroxyAceclofenac and to a number of other metabolites including 5-hydroxyAceclofenac, 4'-hydroxydiclofenac, diclofenac and 5-hydroxydiclofenac. 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 of 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients: Hydroxy Propyl Methyl Cellulose (HPMC) BP/Ph.Eur, Ethyl Cellulose BP/Ph.Eur, Povidone (PVPK 30) BP/Ph.Eur, Isopropyl Alcohol BP/Ph.Eur, Purified Talc BP/Ph.Eur, Magnesium Stearate (Veg Grade) BP/Ph.Eur, Polyethylene Glycol (PEG 6000) BP/Ph.Eur, Titanium Dioxide BP/Ph.Eur, Methylene Chloride Ph.Eur.

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

24 Months.

6.4. Special Precautions for Storage

Store below 30°C, in a dry place.

KEEP ALL MEDICINES AWAY FROM CHILDREN.

6.5. Nature and Contents of Container

ZERODOL - CR (Aceclofenac Controlled Release Tablets 200 mg) are Packed in blister strip of 10 tablets, 1 such blister packed in a printed show box 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 Limited,

Plot No. 255/1, Village-Athal,

Silvassa 396230, Union Territory of Dadra & Nagar Haveli

and Daman & Diu, India

9. NAFDAC REGISTRATION NUMBER (S)

A4-5631