RILIF PLUS
ACECLOFENAC & PARACETAMOL TABLETS

Furthermore, hypo or hyperglycaemia 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.

Potential hepatotoxicity of Paracetamol may be increased by large doses or long-term administration of barbiturates, carbamazepine, hydantoins, isoniazid, rifampin and sulfinpyrazone.

General:

- 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instances, where gastrointestinal bleeding or ulceration occurs in patients receiving Aceclofenac, the drug should be withdrawn.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.
- 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.
- As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.
- 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.
- Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive Paracetamol use, although reports of this event are rare. Reports almost invariably involve cases of severe chronic alcoholics and the dosages of Paracetamol most often exceed recommended doses and often involve substantial overdose. Caution should be taken in patients who regularly consume large amounts of alcohol. Such patients should not exceed the maximum recommended doses of Rilif Plus.

Pregnancy:

The drug in not recommended in pregnant women.

Lactation:

The drug in not recommended in breast-feeding women.

Paediatric use:

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

UNDESIRABLE EFFECTS:

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, haematemesis, 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 reportd 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 disoroders - Aggravated asthma.

Skin and subcutaneous tissue disorder - Toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, photosensitivity reaction.

Renal and urinary disorders - Interstitial nephritis.

General disorders and administration site conditions - Malaise.

Paracetamol:

Hematologic: Hemolytic anemia, neutropenia, leukopenia, pancytopenia, thrombocytopenia.

Hypersensitivity: Skin eruptions, urticaria, erythema, fever.

Miscellaneous: Hypoglycemic coma, jaundice.

OVERDOSAGE:

There are no published reports of overdose with Rilif Plus. In cases of overdose, the stomach should be emptied promptly by lavage or by induction of emesis. Standard supportive measures should be adopted as required.

STORAGE AND HANDLING INSTRUCTIONS:

Store below 30°C. Protect from light & moisture.

PACKAGING INFORMATION:

Rilif Plus is available in a Box of 3 Blisters of 10 Tablets, Box of 1 Blister of 10 Tablets & Box of 10 Blisters of 10 Tablets.

Keep all the medicines away from reach of children.

For further information, please contact:
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PU0540C

For the use of only Registered Medical Practitioners or a Hospital.

RILIF PLUS
ACECLOFENAC & PARACETAMOL TABLETS

POM

COMPOSITION:
Each uncoated tablet contains:
Aceclofenac BP . . . . . 100 mg
Paracetamol BP . . . . . 500 mg
Excipients . . . . . q.s.

DOSAGE FORM:
Tablets for oral use.

DESCRIPTION:
Aceclofenac is an orally administered phenylacetic acid derivative with effects on a variety of inflammatory mediators. It is from the class of non-steroidal anti-inflammatory drug (NSAID), related to diclofenac. Through its analgesic and anti-inflammatory properties, Aceclofenac provides symptomatic relief in a variety of painful conditions.
Paracetamol is a non-opiate, non-salicylate analgesic and antipyretic.

PHARMACOLOGY:
Pharmacodynamics:
Aceclofenac:
Aceclofenac is a novel 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.

1. 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 cyclooxygenase (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.
2. 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.
3. Aceclofenac inhibits Neutrophil Adhesion & Accumulation at the inflammatory site in the early phase and thus blocks the pro-inflammatory actions of Neutrophils.

Paracetamol:
Paracetamol is a peripherally acting analgesic and is well absorbed orally.
Paracetamol produces analgesia by elevation of the pain threshold and antipyresis through action on the hypothalamic heat-regulating center.
Paracetamol is equal to aspirin in analgesic and antipyretic effectiveness.

Pharmacokinetics:
Aceclofenac:
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.
Paracetamol:
The plasma elimination half-life ranges from 1 to 4 hours for Paracetamol. Paracetamol is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drugs is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

INDICATIONS:
Rilif Plus is indicated for the treatment of acute painful inflammatory conditions with or without associated fever.

DOSAGE AND ADMINISTRATION:
Rilif Plus tablets are supplied for oral administration in adults. The maximum recommended dose of Rilif Plus is two tablets daily, taken as one tablet in the morning and one in the evening.

CONTRAINDICATIONS:
- Hypersensitivity to Aceclofenac or Paracetamol or any component of the tablet.
- In patients in whom substances with a similar action (e.g. aspirin, or other NSAIDs), precipitate attacks of asthma, bronchospasm, acute rhinitis or urticaria or patients are hypersensitive to these drugs.
- Severe heart failure or severely impaired hepatic or renal organ function and during the last three months of pregnancy.

WARNINGS AND PRECAUTIONS:
Drug interactions:
Drug interactions associated with Rilif Plus 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.