RUFENAL

Ampoule, Tablets & Suppositories

Composition

Rufenal Injection
Each ampoule of 3 ml contains Diclofenac sodium 75 mg.

Rufenal 12.5 Suppositories
Each suppository contains Diclofenac sodium 12.5 mg.

Rufenal 50 Suppositories
Each suppository contains Diclofenac sodium 50 mg.

Rufenal 100 Suppositories
Each suppository contains Diclofenac sodium 100 mg.

Rufenal 50 Tablets
Each enteric-coated tablet contains Diclofenac sodium 50 mg.

Rufenal 100 Tablets (S.R.)
Each sustained-release tablet contains Diclofenac sodium 100 mg.

Action

Rufenal contains a non - steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties.

Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having an important bearing on its mechanism of action. Prostaglandins play a major role in the causation of inflammation, pain, and fever.

In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of joints, as well as by an improvement in function. In post-traumatic and post-operative inflammatory conditions, Diclofenac rapidly relieves both spontaneous pain and pain on movement and diminishes inflammatory swelling and wound edema.

In clinical trials, Diclofenac was found to exert a pronounced analgesic effect in moderately and severely painful states of non-rheumatic origin. In **a**ddition, clinical studies have revealed that in primary dysmenorrhoea Diclofenac is capable of relieving the pain and reducing the extent of bleeding.

Pharmacokinetics
Absorption
Absorption is complete but onset is delayed until passage through the stomach, which may be affected by food which delays stomach emptying. The mean peak plasma diclofenac concentration reached at about 2 hours (50mg dose produces 1.48 ± 0.65µg/ml (1.5µg/ml ≡5µmol/l)).

Bioavailability:
About half of the administered diclofenac is metabolised during its first passage through the liver ("first-pass" effect), the area under the concentrations curve (AUC) following oral administration is about half that following an equivalent parenteral dose.

Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.

Distribution
The active substance is 99.7% protein bound, mainly to albumin (99.4%).

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose (see section 4.6 Pregnancy and lactation).

Metabolism
Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination
The total systemic clearance of diclofenac in plasma is 263 ± 56 mL/min (mean value ± SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.

About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Indications

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis; juvenile rheumatoid arthritis; ankylosing spondylitis; osteoarthrosis; and spondylarthritis.
- Painful syndromes of the vertebral column.
- Non-articular rheumatism.
- Acute attacks of gout.
- Painful post-traumatic and post-operative inflammation and swelling, e.g. following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis.
- As an adjuvant in severe painful inflammatory infections of the ear, nose, or throat, e.g. pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate.
- Fever alone is not an indication.
- Renal colic and biliary colic.

Contraindications

- Peptic ulcer.
- Hypersensitivity to the active substance.
- Like other non-steroidal anti-inflammatory agents, Diclofenac is also contra-indicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or by other drugs with prostaglandin-synthetase inhibiting activity.
- Suppositories: proctitis.

Warnings and Precautions

Strict accuracy of diagnosis and close medical surveillance are imperative in patients with symptoms indicative of a gastro-intestinal disorder, with a case history suggestive of gastrointestinal ulceration, with ulcerative colitis or with Crohn's disease, as well as in patients suffering from severe impairment of hepatic function.

Owing to the importance of prostaglandins for maintaining renal blood flow, particular caution is needed when using Diclofenac in cases of impaired cardiac or renal function, in patients being treated with diuretics, and in those recovering from major surgical operations.

In the rare instances where peptic ulceration or gastro-intestinal bleeding occurs in patients receiving the medication, the drug should be withdrawn.
In patients of advanced age, caution is indicated on basic medical grounds.

During prolonged treatment with Diclofenac, as with other highly active non-steroidal anti-inflammatory agents, blood counts and monitoring of hepatic and renal function are indicated as precautionary measures.

Pregnancy
Category B (1st and 2nd trimesters)
Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category D (If used in 3rd trimester)
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.

Nursing Mothers
Following oral doses of 50 mg administered every 8 hours, the active substance passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

Adverse Reactions

Gastro-intestinal tract
Occasional: epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea); local irritation (only with suppositories).
Rare: gastro-intestinal bleeding, peptic ulcer.
In isolated cases: peptic ulcer with perforation, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbation of ulcerative colitis).
Exacerbation of haemorrhoids (only with suppositories).

Central nervous system
Occasional: headache, dizziness, or vertigo
Rare: drowsiness.
In isolated cases: disturbances of sensation or vision (blurred vision, diplopia), tinnitus, insomnia, irritability, convulsions.

Skin
Occasional: rashes or skin eruptions.
Rare: urticaria.
In isolated cases: bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, loss of hair, photosensitivity reaction.

Kidney
In isolated cases: acute renal insufficiency, urinary abnormalities (e.g. haematuria),interstitial nephritis, nephrotic syndrome.

Liver
Rare: liver function disorders including hepatitis with or without jaundice, in isolated cases fulminant.

Blood

In isolated cases: thrombocytopenia, leukopenia, agranulocytosis, haemolytic anaemia, aplastic anemia.

Other organ systems
Rare: edema, hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).

Drug Interactions

Diclofenac/ Aspirin
Diclofenac has been reported to depress salicylate levels; the clinical relevance of this is not yet clear.

Diclofenac/ Coumarin Anticoagulants/Oral Hypoglycemics
Pharmacodynamic studies have shown no potentiation of anticoagulant or oral hypoglycemic drugs by Diclofenac. Nevertheless, since other NSAID's do cause such a potentiation, caution should be exercised.

Diclofenac/ Methotrexate
The possibility of fatal interaction between Diclofenac and methotrexate may exist.

Diclofenac/ Lithium
Diclofenac has increased steady-state plasma levels of lithium. Therefore, lithium levels should be monitored when initiating, adjusting and discontinuing Diclofenac.

Diclofenac/ Digoxin
Diclofenac has increased steady-state plasma levels of digoxin. Therefore, digoxin levels should be monitored when initiating, adjusting and discontinuing Diclofenac.

NSAID's/ Probenecid
Probenecid may increase the plasma levels of some NSAID's. The possibility of a drug interaction with Diclofenac exists.

Diclofenac/ Diuretics
Diclofenac is liable to inhibit the activity of diuretics of the furosemide type and to potentiate the effect of potassium-sparing diuretics, thus making it necessary to monitor the serum potassium levels.

Diagnostic Interference
Diclofenac may cause abnormal liver function tests.

Dosage and Administration

Adults
Tablets and suppositories
As a rule, the initial daily dosage is 100-150 mg in milder cases, as well as for long-term therapy, 75-100 mg daily is usually sufficient.

The daily dosage should generally be prescribed in 2-3 fractional doses. To suppress nocturnal pain and morning stiffness, treatment with tablets during the day can be supplemented by the administration of a suppository at bedtime (up to a maximum daily dose of 150 mg).

In primary dysmenorrhoea the daily dosage, which should be individually adapted, is generally 50-150 mg. Initially a dose of 50-100 mg should be given and, if necessary, raised in the course of several menstrual cycles up to a maximum of 200 mg/day. Treatment should be started upon symptomatology, continued for a few days.

Where the symptoms are most pronounced during the night or in the morning, Rufenal S.R. tablets should preferably be taken as 1 tablet daily in the evening, combined if necessary with other forms of Rufenal during the day up to a maximum daily dosage of 150 mg.

The tablets should be swallowed completely with liquid, preferably before meals.

Injection
The dosage is generally one ampoule daily, injected deep intragluteally into the upper outer quadrant. By way of exception, in severe cases (e.g. colic) two injections, separated by an interval of a few hours, can be given per day (one into each buttock).

Alternatively, it is possible to combine one ampoule with other dosage forms of Rufenal up to a maximum daily dosage of 150 mg. Rufenal ampoules should not be given for more than two days; if necessary, the treatment can be continued with other forms of Rufenal.

Children
Children aged 1 year or over should be given 0.5-2 mg/kg body weight daily, in 2-3 fractional doses, depending on the severity of the disorder. For treatment of juvenile rheumatoid arthritis, the daily dosage can be raised up to a maximum of 3 mg/kg, in divided doses.

Rufenal 12.5 suppositories are the most convenient dosage form for use in children.
The dosage strengths are such that Rufenal tablets of 50 mg and suppositories of 50 and 100 mg are not recommended for use in children. Rufenal ampoules are not suitable for children.

Over Dosage
Management of acute poisoning with non-steroidal anti-inflammatory agents consists essentially of supportive and symptomatic measures. There is no typical clinical picture resulting from an over dosage of Diclofenac.

The therapeutic measures to be taken in cases of over dosage are as follows:
Absorption should be prevented as soon as possible after over dosage by means of gastric lavage and treatment with activated charcoal.
Supportive and symptomatic treatment should be given for complications such as hypertension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression.
Specific therapies such as forced diuresis, dialysis, or hemoperfusion are probably of no help in eliminating non-steroidal antirheumatic agents, because of their high protein-binding rate and extensive metabolism.

Presentation
Rufenal Injection
Box of 5 ampoules.

Rufenal 12.5 Suppositories
Box of 6 suppositories.

Rufenal 50 Suppositories
Box of 12 suppositories.

Rufenal 100 Suppositories
Box of 12 suppositories.

Rufenal 50 Tablets
Box of 30 tablets.

Rufenal 100 Tablets (S.R.)
Box of 10 tablets.