VOREN® SUPPOSITORIES

Ingredient(s):
Voren Suppositories 12.5mg: Each supp. contains:
Diclofenac Sodium..... 12.5mg
Voren Suppositories 25mg: Each supp. contains:
Diclofenac Sodium..... 25mg
Voren Suppositories 50mg: Each supp. contains:
Diclofenac Sodium..... 50mg

Pharmacology (Summary of Pharmacodynamic and Pharmacokinetics):
1. Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It also has some uricosuric effect. Diclofenac inhibits cyclo-oxygenase activity with a reduction in the tissue production of prostaglandins such as Prostaglandin F_{2a} and Prostaglandin E_2. The anti-inflammatory effect, measured in the adjuvant-induced arthritis model, is greater than that of aspirin and similar to indomethacin.
   Diclofenac causes gastric erosions and prolongs the bleeding time.
2. Although Diclofenac Sodium does not alter the cause of the underlying disease, it has been found to relieve pain, reduce fever, swelling, and tenderness, and increase mobility in patients with rheumatic of the types indicated.
3. The rectally administered Diclofenac Sodium is rapidly and almost completely absorbed and distributed to blood, liver and kidneys. The plasma concentration shows a linear relationship to the amount of drug administered.
4. The plasma AUC values for unchanged Diclofenac Sodium following rectal administration are within the same range as those of the oral doses of enteric coated tablets.

Indication(s):
Chronic rheumatic arthritis, degenerative osteoarthritis and painful post-operative inflammation.

Dosage and Administration:
Adult: 100mg, usually to be used at night. Maximum total daily dose is 150mg.
Children: 0.5 – 2mg/kg body weight daily, in 2 – 3 divided doses.
Special populations:
Established cardiovascular disease or significant cardiovascular risk factors
The use of high dose diclofenac (150mg/day) for more than 4 weeks is contraindicated in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If diclofenac treatment is needed, patients with established cardiovascular disease, uncontrolled hypertension or significant cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated only after careful consideration and at doses ≤100mg daily if the treatment is for more than 4 weeks. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, diclofenac should always be prescribed at the lowest effective daily dose and for the shortest duration possible.
To be inserted deep into the rectum.
To be dispensed by the physician's prescription.

Contraindication(s):
1. Voren suppository should not be used in patients who have shown hypersensitivity to Diclofenac Sodium.
2. It is contraindicated in patients with any inflammatory lesions of the rectum or anus, and in patients with recent history of rectal and anal bleeding.
3. It should not be given to children under 12 months of age.
4. It is contraindicated in patients with active or suspected peptic ulcer or gastric-intestinal bleeding.
5. It is contraindicated in patients in whom attack of asthma, urticaria or acute rhinitis are precipitated by aspirin or other NSAIDs.
6. The use of high dose diclofenac (150mg/day) for more than 4 weeks is contraindicated in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension.

Side Effect(s) / Adverse Reaction(s):
Local irritation, itching, burning and increased bowel movement.

Central nervous system	: dizziness, headache, insomnia, drowsiness.
Hematologic system	: hemolytic anemia, aplastic anemia, agranulocytosis.
Dermatologic system	: rash, pruritis, skin eruptions, eczema, urticaria and erythema.
Hepatic	: jaundice, hepatitis.
Ophthalmological	: blurred vision.
Allergic	: hypersensitivity reaction.
Cardiac disorders	: Uncommon* : Myocardial infarction, cardiac failure, palpitations, chest pain **The frequency reflects data from long-term treatment with high dose (150mg/day)*
Arteriothrombotic events	: Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150mg daily) and during long-term treatment.

Precaution(s) / Warning(s):
1. Caution should be exercised in patients with a history of blood dyscrasias or disorders of coagulation.
2. Fluid retention and edema have been reported. Voren should be used with caution in patients with cardiac decompensation, hypertension, and renal disease.
3. The anti-inflammatory, antipyretic, and analgesic effects of Voren may mask the normal signs of infections. The physician should be alert to any development of infection in patients receiving Voren.
4. Patients with severe hepatic, cardiac or renal insufficiency or the elderly should be kept under close surveillance.
5. Use of diclofenac in patients with hepatic porphyria may trigger an attack.
6. Severe cutaneous reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis (Lyell's Syndrome), and photosensitivity reactions have been reported.
7. Cardiovascular effects:
   Treatment with NSAIDs, including diclofenac, particularly at high dose and in long term, may be associated with a small increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke).
   As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks. Patients should be advised to remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Use in pregnancy & Lactation:
1st and 2nd Trimesters: Pregnancy Category B: Animals studies have shown no risk for the fetus, but no controlled studies in pregnant women are available.
3rd Trimester: Pregnancy Category D: Voren should not be given during the 3rd trimester owing to the risk of premature closure of the ductus arteriosus and suppression of uterine contractibility.
Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.
Following 2 oral doses of 75mg or 2 oral doses of 50mg given at 8-hr intervals, the active substance passes into the breast milk, but in such small quantities that no unwanted effects on the infant are likely to occur.

WARNINGS

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor GI problems (eg. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper GI ulcers, gross bleeding or perforation occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for 1 year. Higher percentages have been reported by other independent studies.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease, (eg. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.
Measures such as the use of physical therapy and mild analgesics like Paracetamol (when inflammation is not a major factor) should be instituted prior to initiation of therapy with NSAID. NSAIDs should only be used after proper appraisal of potential risks to patients. It should be used with the lowest effective dose for only as long as needed. This drug should not be co-administered with other NSAIDs. Prescribers should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should offset the potential increased risk of GI toxicity.

Drug Interaction(s):
The drug has an affinity for serum albumin, and may displace other drugs which are also bound to albumin. Concomitant treatment with Potassium sparing diuretics may be associated with increased serum Potassium level. Concomitant administration with Aspirin is not recommended because Voren is displaced from binding site and resulting in lower plasma concentration and peak plasma levels. Concurrent therapy with Voren and Warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required. Patients with altered renal function should be observed for the development of the specific toxicities of concomitant administration of Voren and Digoxin, Methotrexate and Cyclosporine. Patients receiving oral hypoglycemic should be observed for signs of toxicity to these drugs.

Symptoms and Treatment for Overdosage, and Antidote(s):
Symptoms of overdose reported have generally reflected, the renal and CNS toxicities of this medication. More serious overdosage effects such as, acute renal failure, convulsion and coma have been reported.
Should accidental overdosage occur, supportive and symptomatic treatment is indicated for complication, eg. hypotension, renal failure, convulsions and respiratory depression. Because it is firmly bound to plasma proteins, hemodialysis and peritoneal dialysis may be of little value.

Shelf-Life:
3 years from the date of manufacture.

Storage Condition(s):
Store at temperature below 25°C. Protect from light and moisture.

Product Description(s) & Packing(s):
Voren Suppositories 12.5mg:
White to a pale yellow, bullet-shaped suppositories.
10 supp. per strip, 10 strips per box.
Voren Suppositories 25mg:
White to a pale yellow, bullet-shaped suppositories.
10 supp. per strip, 10 strips per box.
Voren Suppositories 50mg:
White to a pale yellow, bullet-shaped suppositories.
10 supp. per strip, 10 strips per box.

Y. S. P.®

Manufacturer and Product Registration Holder:
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