Votan SR Film Coated Tablets 100 mg "S.T"

[INGREDIENT]
Each SR F.C. Tablet contains:
Diclofenac sodium.....100 mg

[DESCRIPTION]
It is a pale sunset yellow, biconvex film-coated tablet.

[ROUTE OF ADMINISTRATION]
Oral

[PHARMACODYNAMIC]
Votan SR F.C. Tablets 100 mg "S.T" contains a non-steroidal compound with pronounced antirheumatic, and anti-inflammatory, analgesic, and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated experimentally, is regarded as having as important bearing on its mechanism of action.

[PHARMACOKINETICS]
Diclofenac is completely absorbed from the sustained-release tablets. As a result of delayed release of the active substance, the peak plasma concentrations attained are lower than those achieved following the administration of conventional dosage forms. On the other hand, concentrations remain measurable for some hours after attaining their peak. Absorption sets in later following ingestion of a sustained-release tablet either with or after a meal than it does following administration on an empty stomach. Since about half the active substance is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) is about half as large following oral or rectal administration as it is following a parenteral dose of equal size. Pharmacokinetic behaviour remains unchanged following repeated administration. No accumulation occurs provided the recommended dosage intervals are observed. Diclofenac enters the synovial fluid, where maximum concentration 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. Only 4-6 hours after administration, therefore, 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. The biotransformation of diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylation followed by glucuronidation. About 60% of the administered dose is excreted in the urine in the form one of these two processes; less than 1% excreted as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the feces.
No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.
In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 ml/min, the theoretical steady-state plasma levels of metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile. In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis), the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

[INDICATIONS]
- Inflammatory and degenerative forms of rheumatism; rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis
- Painful syndromes of the vertebral column;
- Non-articular rheumatism;
- Painful post-traumatic and postoperative inflammation and swelling;
- Primary dysmenorrhoea.

[DOSAGE AND ADMINISTRATION]
1 tablet of Votan SR daily.
Where the symptoms are most pronounced during the night or in the morning, Votan SR should preferably be taken in the evening.
The tablets of Votan SR should neither be fragmented nor chewed. They should be taken with liquid, preferably at mealtimes.
As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNINGS AND PRECAUTIONS).

Established cardiovascular disease or significant cardiovascular risk factors
Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ishemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, daibetes mellitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≥100 mg daily if treated for more than 4 weeks (see section WARNINGS AND PRECAUTIONS).

[CONTRAINDICATIONS]
- Peptic ulcer.
- Hypersensitivity to the active substance.
- Like other non-steroidal anti-inflammatory agents. Votan is also contraindicated 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. 'Last trimester of pregnancy-severe hepatic renal and cardiac failure'
- Severe cardiac failure (see section WARNINGS AND PRECAUTIONS).

[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 gastro-intestinal 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 called for when using Votan 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 occur in patients receiving the medication, the drug should be withdrawn.

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

Severe cutaneous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs.

Warning 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 upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescibers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patient 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 (e.g. alcoholism, smoking, and corticosteroid therapy) are increased risk. Elderly or debilitated patients seems to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Cardiovascular effects
Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, maybe associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke).
Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension, or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) shoud be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks.

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 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.

Gastrointestinal effects
NSAIDs, including diclofenac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastrointestinal surgery.

Pediatric and Geriatric use
Votan is not suitable for children.
In patients of advanced age, caution is indicated on basic medical grounds.

Effects on ability to drive or use machines
Patients experiencing dizziness or other central nervous disturbance should refrain from driving a vehicle or operating machines.

[PREGNANCY AND LACTATION]
During pregnancy Votan should be employed only for compelling reasons and only in the lowest effective doses. As in the case of other prostaglandin-synthetase inhibitors, this applies particularly to the last 3 months of pregnancy (owing to the responsibility of uterine inertia and/or premature closure of the ductus arterious).
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 desirable effects on the infant are to be expected.

[DRUG INTERACTIONS]
When given together with preparations containing lithium or digoxin, diclofenac may raise their plasma concentrations; but no clinical signs of overdosage in such cases have yet been encountered.
Various non-steroidal anti-inflammatory agents are liable to inhibit the activity of diuretics. Concomitant administration of systemic non-steroidal anti-inflammatory agents or glucocorticoids may increase the occurence of side effects.
Clinical investigations would appear to indicate that Votan has no influence on the effect of oral anticoagulants. As a precaution, however, it is recommended that, when giving concomitant treatment with Votan and anticoagulants, laboratory tests should be performed in order to check that the desired response to the anticoagulants is being maintained.
As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose (200 mg) can temporarily inhibit platelet aggregation.
Clinical studies have shown that Votan can be given together with oral antidiabetic agents without influencing their clinical effect.
Caution should be exercised when non-steroidal anti-inflammatory drugs are administered less than 24 hours before or after treatment with methotrexate, since the blood concentration of methotrexate may rise and the toxicity of this substance be increased.

[ADVERSE REACTIONS]
Gastro-intestinal tract:
Occasional: epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea).
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).

Central nervous system:
Occasional: headache, dizziness, or vertigo.
Rare: drowsiness.
In isolated cases: disturbance 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, Steven-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, leucopenia, agranulocytosis, haemolytic anaemia, aplastic naemia.

Dermatological:
Occasional: rashes or skin eruptions. Cases of hair loss, bullous eruptions, erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported

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

Cardiac disorders:
Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain.
*The frequency reflects data from long-term treatment with a high dose (150 mg/day).

Kounis syndrome：Frequency "not known"

Description of selected adverse drug reactions

Arteriothrombotic events
Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and durimg long-term treatment (see section WARNINGS AND PRECAUTIONS).

[OVERDOSAGE]
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 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, gastro-intestinal irritation, and respiratory depression.
Specific therapies such forced diuresis, dialysis, or haemoperfusion are probably of no help in eliminating non-steroidal anti-inflammatory agents, because of their high protein-binding rate and extensive metabolism.

[SHELF LIFE]
3 Years

[STORAGE CONDITION]
Store below 30ºC, and protect from light and moisture.

[PACKAGE]
10 x 10 tablets in PVC/foil blister strip/box.

REGISTRATION NO.: MAL10070587AZ

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Revised Date: 21 Apr 2022