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In patients with poor liver function, delayed, elevated and prolonged circulating levels of the sulfide and sulfone metabolites may occur. Such patients should be monitored closely: a reduction of the daily dosage may be required.

Cases of hepatitis, jaundice, or both, with or without fever, may occur within the first three months of therapy. In some patients, the findings are consistent with those of cholestatic hepatitis.

Fever and other evidence of hypersensitivity including abnormalities in one or more liver function tests and skin reactions have occurred during therapy with CLINORIL. Fatalities have occurred in some of these patients.

Hypersensitivity syndrome: A potentially life-threatening apparent hypersensitivity syndrome has been reported. In cases where this syndrome is suspected, therapy should be discontinued immediately and not reinstituted. This syndrome may include constitutional symptoms (fever, chills, diaphoresis, flushing) cutaneous findings (rash or other dermatologic reactions (see Side Effects), conjunctivitis, involvement of major organs (changes in liver function tests, hepatic failure, jaundice, pancreatitis, pneumonia, with or without pleural effusion, leukopenia, leukocytosis, eosinophilia, disseminated intravascular coagulation, anemia, renal impairment, including renal failure and other less specific findings (adenitis, arthralgia, arthritis, myalgia, fatigue, malaise, hypotension, chest pain, tachycardia).

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**composition**

Tablets of 200 mg Sulindac.

**activity**

CLINORIL is a prostaglandin synthetase inhibitor with anti-inflammatory and analgesic activities.

**indication**

Osteoarthritis, rheumatoid arthritis, bursitis, tendinitis and tenosynovitis.

**dosage and method of administration**

To be taken once or twice a day with fluids or food. The appropriate dosage and duration of treatment will be recommended by the physician. Adults: usual daily dosage may vary from 200 mg - 400 mg. The twice daily dosage regimen may be tried in patients that do not tolerate the single daily dosage well. Doses above 400 mg per day are not recommended.

**contraindications**

Hypersensitivity to any component of this product. CLINORIL should not be used in patients in whom acute asthmatic attacks, urticaria or rhinitis have been precipitated by acetylsalicylic acid or other prostaglandin synthetase inhibitors.

The drug should not be administered to patients with active gastrointestinal bleeding. The use of CLINORIL should be avoided in patients with active peptic ulcer.

CLINORIL should not be given to children.

**warnings and precautions**

**gastrointestinal effects:** CLINORIL should be used with caution in patients having a history of gastrointestinal hemorrhage or ulcers.

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Significant (three times the upper limit of normal) elevations of SGPT (ALAT) or SGOT (ASAT) occurred in controlled clinical trials in less than 1% of patients receiving this therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy.

Renal effects: In patients with an history of renal dysfunction it is recommended to check renal function regularly.

Sulindac metabolites have been reported rarely as the major or a minor component in renal stones in association with other calculus components. CLINORIL should be used with caution in patients with a history of renal lithiasis and they should be kept well hydrated while receiving CLINORIL.

Effect on the ability to drive and operate machinery
No data are known about the effect of this product on the ability to drive. Side effects like dizziness, drowsiness, neurologic disorders and visual disturbances may affect the ability to drive.

Drug interactions
Dimethyl sulfoxide: DMSO (dimethyl sulfoxide) should not be used with sulindac. Concomitant administration has been reported to reduce the plasma levels of the active sulfide metabolite and may potentially reduce efficacy. In addition this combination has been reported to cause peripheral neuropathy.

Methotrexate: caution should be used if sulindac is administered simultaneously with methotrexate. Prostaglandins synthetase inhibitors have been reported to decrease the tubular secretion of methotrexate and to potentiaste the toxicity.

Ciclosporin: administration of prostaglandins synthetase inhibitors concomitantly with ciclosporin has been associated with an increase in ciclosporin-induced toxicity. Prostaglandin synthetase inhibitors should be used with caution in patients taking ciclosporin, and renal function should be monitored carefully.

Acetylsalicylic acid: the concomitant administration of acetylsalicylic acid with sulindac in normal volunteers significantly depressed the plasma levels of the active sulfide metabolite. In a clinical study, the combination showed an increase in the incidence of gastrointestinal side effects. Since the addition of acetylsalicylic acid did not have a favourable effect on the therapeutic response to CLINORIL, the combination is not recommended.

Probenecid: Probenecid given concomitantly with sulindac had only a slight effect on plasma sulfide levels, while plasma levels of sulindac and sulfone were increased. Sulindac was shown to produce a modest reduction in the uricosuric action of Probenecid, which probably is not significant under most circumstances.

Oral anticoagulants and hypoglycemic agents: although sulindac and its sulfide metabolite are highly bound to protein, studies in which CLINORIL was given at a dose of 400 mg daily have shown no clinically significant interaction with oral anticoagulants or oral hypoglycemic agents. However, patients should be monitored carefully until it is certain that no change in their anticoagulant or hypoglycemic dosage is required.

Diflunisal: The concomitant administration of CLINORIL and diflunisal in normal volunteers resulted in lowering of the plasma levels of the active sulindac metabolite by approximately one-third.

Dextropropoxyphene and paracetamol: neither dextropropoxyphene nor paracetamol had any effect on the plasma levels of sulindac or its sulfide metabolites.

Antacids: in a drug interaction study, an antacid (magnesium and aluminium hydroxides, in suspension 30 ml) was administered with CLINORIL with no significant difference in absorption.

Antihypertensive agents: To date no interaction between sulindac and a variety of antihypertensives has been noted. However, the blood pressure of patients taking CLINORIL with antihypertensive agents should be closely monitored.

The patient should inform the doctor of any medica-
Pregnancy and lactation

There are insufficient data to evaluate the possible harmfulness of this substance when used in human pregnancy. To date, there has been no evidence of harmfulness in animal trials. CLINORIL should not be given to pregnant women, since safety for its use has not been established. The known effects of drugs of this class during the third trimester of pregnancy are inhibition of labor, and on the human fetus closure of the ductus arteriosus, platelet dysfunction with resultant bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation and myocardial degenerative changes. CLINORIL should not be given to lactating women since safety for this use has not been established.

Side effects and any problem that may occur

Gastrointestinal: the most frequent types of side effects occurring with CLINORIL are gastrointestinal; these include gastrointestinal pain, dyspepsia, nausea with or without vomiting, diarrhea, constipation, flatulence, anorexia and gastrointestinal cramps. Dermatologic: rash, pruritus. Central nervous system: dizziness, headache, nervousness. Special senses: tinnitus. Miscellaneous: edema. Side effects reported less frequently: the probability exists of a causal relationship between CLINORIL and these side effects. Gastrointestinal: stomatitis, gastritis, or gastroenteritis. Peptic ulcer, colitis, gastrointestinal bleeding and GI perforations have been reported. Fatalities have occurred. Liver function test abnormalities, jaundice sometimes with fever, cholestasis, hepatitis, hepatic failure, pancreatitis, ageusia, and glossitis. It has also been reported that a probable sulindac metabolite has been found in biliary sludge in patients with symptoms of cholecystitis who underwent a cholecystectomy. Dermatologic: sore and dry mucous membranes, alopecia, photosensitivity, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis. Cardiovascular: congestive heart failure especially in patients with marginal cardiac function, palpitation, hypertension. Hematologic: thrombocytopenia, ecchymosis, purpura, leukopenia, agranulocytosis, neutropenia, bone marrow depression, including aplastic anemia, hemolytic anemia, increased prothrombin time in patients on oral anticoagulants. Genitourinary: urine discoloration, dysuria, vaginal bleeding, hematuria, proteinuria, crystalluria, renal impairment, including renal failure, interstitial nephritis, nephrotic syndrome. Nervous system: vertigo, somnolence, insomnia, sweating, asthenia, paresthesia, convulsions, syncope, depression, psychic disturbances including acute psychosis, aseptic meningitis. Metabolic: hyperkalemia. Musculoskeletal: muscle weakness. Special senses: visual disturbances including blurred vision, decreased hearing, metallic or bitter taste. Respiratory: epistaxis. Hypersensitivity reactions: anaphylaxis and angio-neurotic edema. Bronchial spasm, dyspnea, hypersensitivity vasculitis, hypersensitivity syndrome (see Warnings & Precautions). Overdosage effects

Cases of overdosage have been reported and rarely fatalities have occurred. The following signs and symptoms may be observed following overdosage: stupor, coma, diminished urine output and hypotension. In isolated cases, patients have received up to 900 mg a day without adverse consequences being reported.

In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Animal studies show that absorption is decreased.
by the prompt administration of activated charcoal and excretion is enhanced by alcalinization of the urine.

**Storage instructions**
As indicated on the outer pack of the product.
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