

# MOBICOL

Tablets

## Composition

Each tablet contains Sulindac 200 mg.

## Action

Sulindac is a non-steroidal, antirheumatic agent possessing anti-inflammatory, analgesic, and anti-pyretic properties.

Prostaglandin synthetase inhibition has been hypothesized to be the basis of the mechanism of action of non-steroidal anti-inflammatory agents. Following absorption, sulindac undergoes two major biotransformation: reversible reduction to the sulfide metabolite, and irreversible oxidation to the inactive sulfone metabolite. The sulfide metabolite is a potent inhibitor of prostaglandin synthesis, and available evidence indicates that the biological activity of sulindac resides with the sulfide metabolite. Thus, the sulfoxide form (sulindac) is a prodrug.

## Onset of Action in Usual Doses

Clinical improvement usually occurs within one week of therapy for osteoarthritis, ankylosing spondylitis and rheumatoid arthritis.

## Pharmacokinetics

Sulindac is approximately 90% absorbed in humans after oral administration. The peak plasma concentrations of the biologically active sulfide metabolite are achieved in about two hours when sulindac is administered in the fasting state, and in about three to four hours when sulindac is administered with food. The mean half-life of sulindac is 7.8 hours, while the mean half-life of the sulfide metabolite is 16.4 hours. Sustained plasma levels of the sulfide metabolite are consistent with a prolonged anti-inflammatory action which is the rationale for a twice per day dosage schedule.

The proportion of sulindac metabolised to the sulfide and the sulfone cannot be obtained in humans, however it is known that more than 20% of the dose of sulindac is converted to the inactive sulfone metabolite since urinary excretion of free and conjugated sulindac sulfone accounts for 21 to 25.6% of the dose. While the active sulfide metabolite is not excreted in the urine to an appreciable extent it is known that following a dose regimen of 200 mg given every 12 hours the ratio of parent medicine to active sulfide metabolite in plasma (AUC ratio) averages about 0.6.

The bioavailability of sulindac tablets, as assessed by urinary excretion, was not changed by concomitant administration of an antacid containing magnesium and aluminum hydroxides.

In patients with poor liver function, delayed, elevated and prolonged circulating levels of the sulfide and sulfone metabolites may occur.

In end stage, renal disease the AUC for unbound sulindac sulfide averaged about one-half that in normal healthy volunteers indicating that net reduction of sulindac to the active metabolite is impaired in end stage renal disease.

Studies of the effects of age and disease on the pharmacokinetics and pharmacodynamics of sulindac report that there is no justification for lowering the recommended dose in patients older than 65 years of age.

Multiple dose pharmacokinetic studies comparing sulindac 400 mg once a day with 200 mg twice a day, found that at steady state the maximum and minimum serum concentrations of the sulfide were not significantly different between the regimens. Moreover when sulindac was administered once daily in the evening, plasma levels of active medicine in the early morning were significantly higher than when administered twice daily.

Sulindac and the sulfone metabolite undergo extensive enterohepatic circulation relative to the sulfide metabolite. The enterohepatic circulation together with the reversible metabolism is probably major contributors to sustained plasma levels of the active medicine.

The primary route of excretion in humans is via the urine as both sulindac and the sulfone metabolite and glucuronide conjugates. Approximately 50% of an oral dose is excreted in the urine, with the conjugated sulfone metabolite accounting for the major portion. Approximately 25% of an oral dose found in the faeces, primarily as the sulfone and sulfide metabolites.

## **Indications**

Mobicol indicated for the symptomatic treatment of the following:

- Rheumatoid arthritis.
- Osteoarthritis.
- Ankylosing Spondylitis.
- Periarticular inflammatory disorders.
- Acute gouty arthritis.

## **Contraindications**

- Patients known to be allergic to Sulindac.
- Patients in whom acute asthmatic attacks, urticaria or rhinitis have been precipitated by aspirin or other non-steroidal anti-inflammatory agents.
- Patients with a history of active gastro-intestinal bleeding or peptic ulceration.
- Sulindac should not be given to children.

## **Warnings**

### **Gastrointestinal**

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID's. Although minor upper gastrointestinal problems, such as dyspepsia, are common and usually develop early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAID's, even in the absence of previous gastrointestinal tract symptoms.

In patients with active gastrointestinal bleeding or an active peptic ulcer, an appropriate ulcer regimen should be instituted. Physicians must weigh the benefits of therapy with Sulindac against the possible hazards, and carefully monitor the patient's progress. When Sulindac is prescribed for patients with a history of upper gastrointestinal tract disease, it should be administered under close supervision, and only when monitoring for potential side effects is undertaken .

Elderly or debilitated patients seem to tolerate, ulceration or bleeding less well than other individuals do, and most spontaneous reports of fatal gastrointestinal events are in this population.

### **Hypersensitivity**

Fever and other evidence of hypersensitivity (including abnormalities in one or more liver function tests and severe skin reactions) have occurred in rare cases during therapy with Sulindac. Fatalities have occurred in these patients. Hepatitis and/or jaundice, with or without fever may occur, usually within the first 1-3 months of therapy. Determinations of liver function should be considered whenever a patient on therapy with Sulindac develops unexplained fever, rash or other dermatological reactions or constitutional symptoms. If unexplained fever or other evidence of hypersensitivity occurs, therapy with Sulindac should be discontinued. The elevated temperature and abnormalities in liver function caused by Sulindac characteristically have reverted to normal after discontinuation of therapy. Administration of Sulindac should not be reinstated in such patients.

### **Renal**

Since primarily the kidneys, patients with, eliminate Sulindac significantly, impaired renal function should be closely monitored, and a low daily dosage should be anticipated to avoid excessive drug accumulation. Such patients should be kept well hydrated while receiving Sulindac.

### **Hepatic**

Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has been reported, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with Sulindac. Although such reactions are rare, if abnormal liver tests persist or worsen, or clinical signs and symptoms consistent with liver disease develop, or systemic manifestation occur (e.g. eosinophilia, rash, etc.), Sulindac should be discontinued.

### **Pregnancy**

#### *Category B (1<sup>st</sup> and 2<sup>nd</sup> 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**

It is not known whether Sulindac is secreted in human milk. However, it is secreted in the milk of lactating rats. Nursing should not be undertaken while a patient is receiving Sulindac.

### **Paediatric Use**

Safety and effectiveness in children have not been established.

### **Adverse Reactions**

Gastro-intestinal side effects are the most common and consist of abdominal pain, nausea, and constipation. Gastro-intestinal ulceration and bleeding may also occur.

The most frequently reported central nervous system side effects are drowsiness, dizziness, headache, and nervousness.

Other adverse effects include depression, tinnitus, confusion, light-headedness, insomnia, psychiatric disturbances, syncope, convulsions, coma, peripheral neuropathy, blurred vision and other ocular effects, edema and mass gain, hypertension, hematuria, skin rashes, pruritus, urticaria, stomatitis, alopecia and hypersensitivity reactions.

A hypersensitivity syndrome consisting of fever and chills, skin rashes or other cutaneous manifestations, hepatotoxicity, renal toxicity (including renal failure), leukopenia, thrombocytopenia, eosinophilia, inflamed glands or lymph nodes, and arthralgia has been reported.

Leucopenia, purpura, thrombocytopenia, aplastic anaemia, haemolytic anaemia, agranulocytosis, epistaxis, hyperglycemia, hyperkalemia, and vaginal bleeding have been reported. There have also been reports of hepatitis and jaundice or renal failure.

### **Precautions**

Although Sulindac has less effect on platelet function and bleeding time than acetylsalicylic acid, it is nevertheless an inhibitor of platelet function. Therefore, patients who may be adversely affected should be carefully observed when Sulindac is administered.

Pancreatitis has been reported in patients receiving Sulindac. Should pancreatitis be suspected, the drug should be discontinued and not restarted. Supportive medical therapy should be instituted, and the patient monitored closely with appropriate laboratory studies (e.g. serum and urine amylase, amylase/Creatinine clearance ratio, electrolytes, serum calcium, glucose, lipase). A search for other causes of pancreatitis, as well as those conditions which mimic pancreatitis, should be conducted.

Because of reports of adverse eye findings with NSAID's, it is recommended that patients who develop eye complaints during treatment with Sulindac undergo ophthalmological examinations.

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

Peripheral edema has been observed in some patients taking Sulindac. Therefore, as with other NSAID's, Sulindac should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

Use of Sulindac may allow a reduction in dosage or the elimination of chronic corticosteroid therapy in some patients with rheumatoid arthritis. However, it is generally necessary to reduce corticosteroids gradually over several months, in order to avoid an exacerbation of the disease or signs and symptoms of adrenal insufficiency. Abrupt withdrawal of chronic corticosteroid treatment is generally not recommended, even when patients have had a serious complication of chronic corticosteroid therapy.

Sulindac may cause drowsiness. Patients should be warned that their ability to perform potentially hazardous tasks requiring mental alertness or physical coordination, such as driving a vehicle or operating machinery, might be impaired.

## **Drug Interactions**

### *Sulindac/ Oral Anticoagulants/ Oral Hypoglycemics*

Although Sulindac and its sulphide metabolite are highly bound to protein, studies in which Sulindac was administered in a dose of 400 mg daily showed no clinically significant interaction with oral anticoagulants or oral hypoglycaemic agents. However, patients should be monitored carefully until it is certain that no change in their anticoagulant or hypoglycaemic dosage is required. Special attention should be paid to patients taking higher than recommended doses, and to patients with renal impairment or other metabolic defects that might increase Sulindac blood levels.

### *Sulindac/Acetylsalicylic Acid*

The concomitant administration of acetylsalicylic acid with Sulindac significantly depresses the plasma levels of the active sulphide metabolite, and increases the incidence of gastrointestinal adverse reactions. Therefore, this combination cannot be recommended.

### *Sulindac/ Diflunisal*

The concomitant administration of Sulindac and diflunisal in normal volunteers resulted in lowering of the plasma levels of the active Sulindac sulphide metabolite by approximately one-third.

### *Sulindac/ Propoxyphene Hydrochloride/ Paracetamol*

Neither propoxyphene hydrochloride nor Paracetamol had any effect on the plasma levels of Sulindac or the sulphide metabolite.

### *Sulindac/ Antacids*

In a drug interaction study and antacid (magnesium and aluminium hydroxides, in suspension) was administered with Sulindac with no significant difference in absorption.

### *Sulindac/ Antihypertensive Agents*

In general, Sulindac does not reduce the antihypertensive effects of a variety of agents used to treat mild to moderate hypertension, in contrast to most other NSAID's. However, the blood pressure of patients taking Sulindac with antihypertensive agents should still be closely monitored.

### *Sulindac/ Probenecid*

Probenecid administered concomitantly with Sulindac has only a slight effect on plasma sulphide levels, while plasma levels of Sulindac and sulfone are increased. Sulindac has been shown to produce a modest reduction in the uricosuric action of probenecid, which is probably insignificant under most circumstances.

*Sulindac/ Dimethylsulfoxide (DMSO)*

DMSO should not be administered together with Sulindac. Concomitant administration has been reported to reduce the plasma levels of the active sulphide metabolite and potentially reduce efficacy. In addition, the combination has been reported to cause peripheral neuropathy.

*Sulindac/ Methotrexate*

Caution should be used if Sulindac is administered concomitantly with methotrexate. NSAID's have been reported to decrease the tubular secretion of methotrexate and potentiate its toxicity.

*Sulindac/ Cyclosporine*

Administration of NSAID's concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAID's should be used with caution in patients taking cyclosporine, and renal function should be monitored carefully.

### **Dosage and Administration**

Mobicol should be administered twice a day, with fluids or food.

The recommended dosage is 100-200 mg. twice a day. In clinical studies to date, 400 mg/day was the maximum dosage administered.

In the treatment of acute gouty arthritis, the recommended dosage is 200 mg twice a day, for 7-10 days.

### **Over Dosage**

In the event of over dosage, the stomach must 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 alkalinization of the urine.

### **Presentation**

Box of 20 tablets.