

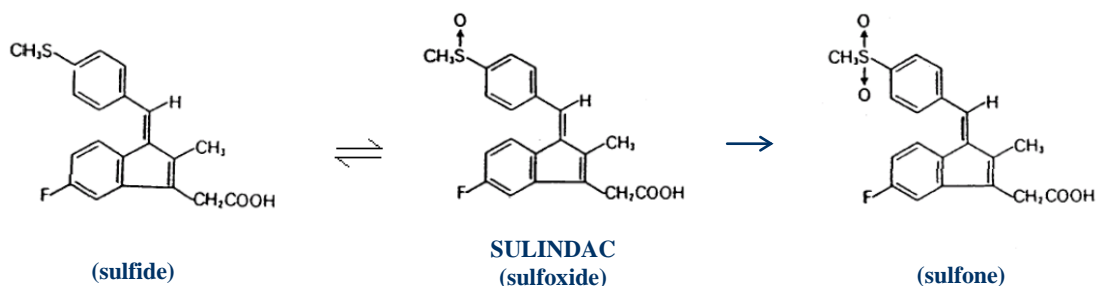
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient: Sulindac

Chemical name: (Z)-5-fluoro-2-methyl-1-[[p-(methyl-sulfinyl)phenyl]methylene]-1H-indene-3-acetic acid

Structural formula: Sulindac and its metabolites



Molecular formula: $C_{20}H_{17}FO_3S$

Molecular weight: 356.42

CAS Registry No.: 38194-50-2

DESCRIPTION

Sulindac is a non-steroidal, anti-rheumatic agent with anti-inflammatory, analgesic and anti-pyretic properties. It is an arylalkanoic acid derivative but is not a propionic acid. Nor is it a salicylate, pyrazolone or corticosteroid.

Sulindac is a non-steroidal anti-inflammatory indene-type compound. Sulindac is a yellow crystalline compound. It is a weak organic acid [pKa (25°C) 4.7]. It is soluble in water as the sodium salt or in buffers of pH 6 or higher but is practically insoluble in water below pH 4.5 and sparingly soluble in alcohol.

Each Aclin and Aclin 200 tablet contains sulindac 100 mg and 200 mg as the active ingredient, respectively. The tablets also contain the following inactive ingredients: lactose, cellulose – microcrystalline, povidone, sodium starch glycollate, quinoline yellow CI47005, talc – purified, magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

Aclin usually provides prompt symptomatic relief of inflammation, pain and tenderness and promotes early restoration of joint mobility. The drug has a prolonged duration of activity which permits a once or twice a day dosage schedule, and be used for long-term treatment. Sulindac has been shown to be an effective, well tolerated compound.

Prostaglandin synthetase inhibition has been hypothesised to be the basis of the mechanism of action of non-steroidal anti-inflammatory agents (NSAIDs). Following absorption, sulindac undergoes two major biotransformations – 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.

Pharmacokinetics

Absorption

Sulindac is approximately 90% absorbed in man 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. Sulindac and its metabolites are extensively (90 to 98%) bound to protein in plasma.

Distribution

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 two dosage regimens. Moreover, when sulindac was administered once daily in the evening, plasma levels of active drug in the early morning hours were significantly higher than when administered twice a day.

Metabolism

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

Excretion

The primary route of excretion in man is via the urine as both sulindac and its sulfone metabolite (free as well as glucuronides), with the sulfone metabolite accounting for the major portion. Less than 1% of the administered dose of sulindac appears in the urine as the sulfide metabolite. Approximately 25% is found in the faeces, primarily as the sulfone and sulfide metabolites. Sulindac, sulfone and the active sulfide metabolite are excreted in the bile and subject to extensive enterohepatic recycling in animals. Further biotransformation of sulindac may take place in the gastrointestinal tract. Similar enterohepatic circulation, together with reversible metabolism are probably major contributors to sustained plasma levels of the active drug in man.

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

INDICATIONS

Aclin is indicated in:

- osteoarthritis
- rheumatoid arthritis
- ankylosing spondylitis
- acute gouty arthritis
- the relief of acute and/or chronic pain states in which there is an inflammatory component.

CONTRAINDICATIONS

Patients who are hypersensitive to any component of this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other NSAIDs.

As with other anti-inflammatory agents, indomethacin may mask the signs and symptoms of peptic ulcer. Because indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract, it should not be given to patients with active peptic ulcer, or with a recurrent history of gastrointestinal ulceration.

Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Use in Pregnancy (see **Precautions - Use in Pregnancy**).

Use in Lactation (see **Precautions - Use in Lactation**).

Patients with severe heart failure.

PRECAUTIONS

Aclin should not be used in patients in whom acute asthmatic attacks, rhinitis or urticaria have been precipitated by aspirin or other non-steroidal anti-inflammatory agents.

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see **Dosage and Administration**).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention or heart failure.

Gastrointestinal Events

All NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increase the risk of serious gastrointestinal adverse events.

The drug should not be administered to patients with active gastrointestinal bleeding.

Aclin should be used with caution in patients with a history of gastrointestinal haemorrhage or ulcers. In patients with an active peptic ulcer, an appropriate therapeutic regimen should be instituted and the physician must weigh the benefits of Aclin against possible hazards (see **Adverse Effects**) and carefully monitor the patient's progress. [In a drug interaction study, an antacid (magnesium and aluminium hydroxides, in suspension, 30 mL) was administered with sulindac with no significant difference in absorption].

Severe Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

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 **Adverse Effects**), conjunctivitis, involvement of major organs (changes in liver function tests, hepatic failure, jaundice, pancreatitis, pneumonitis with or without pleural effusion, leucopenia, leucocytosis, eosinophilia, disseminated intravascular coagulation, anaemia, renal impairment, including renal failure), and other less specific findings (adenitis, arthralgia, arthritis, myalgia, fatigue, malaise, hypotension, chest pain, tachycardia).

Platelet Aggregation

Sulindac is a moderate to weak inhibitor of platelet function and, therefore, patients who may be adversely affected by this (e.g. those undergoing surgery) should be observed closely.

Oral Anticoagulants

Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and warfarin has been associated with severe, sometimes fatal, haemorrhage, especially in the elderly. The exact mechanism is unknown, but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Aclin should be used in combination with warfarin only if absolutely necessary, and patients taking this combination should be closely monitored. Adjustment of dosage for oral anticoagulants may be required.

Oral Hypoglycaemic Agents

Data available from limited animal studies have shown no evidence of interaction of sulindac with oral hypoglycaemic agents. However, Aclin should be used with caution in patients receiving such agents.

Renal Effects

As the drug is mainly excreted in urine, it should be used with caution in patients with impaired renal function. In severe renal failure the dosage may need to be reduced.

As with other non-steroidal anti-inflammatory drugs, long-term administration of sulindac to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been observed in patients with pre-renal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Aclin may affect renal function less than other NSAIDs in patients with chronic glomerular renal disease (see **Pharmacology**). Until these observations are better understood and clarified, however, and because renal adverse experiences have been reported with sulindac (see **Adverse Effects**), caution should be exercised when administering this drug to patients with those conditions associated with increased risk of the effects of non-steroidal anti-inflammatory

drugs on renal function, such as those with renal or hepatic dysfunction, diabetes mellitus, complications associated with advanced age, extracellular volume depletion from any cause, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. A NSAID should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment state.

As Aclin is eliminated primarily by the kidneys, those patients with significantly impaired renal functions should be closely monitored and a lower daily dosage anticipated to avoid excessive drug accumulation.

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

Infections

Nonsteroidal anti-inflammatory drugs, including Aclin, may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing infection.

Corticosteroids

As is the case during therapy with other anti-inflammatory-analgesic-antipyretic drugs, if corticosteroids are reduced or discontinued during therapy with Aclin, the dose of the corticosteroid should be reduced slowly and the patient observed closely for adverse effects, particularly adrenal insufficiency and exacerbation of rheumatoid arthritis.

Hepatic Effects

Significant (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) occurred in controlled clinical trials in less than 1% of patients receiving this therapy.

It is recommended that, in those patients with a history of liver dysfunction, periodic liver function tests be carried out. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy.

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 and a reduction of 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 sulindac. Fatalities have occurred in some of these patients.

Determinations of liver function should be considered whenever a patient on therapy with Aclin develops unexplained fever, rash or other dermatological reactions or constitutional symptoms. If unexplained fever or

other evidence of hypersensitivity occurs, therapy with Aclin should be discontinued. Administration of Aclin should not be reinstituted in such patients.

The elevated temperature and abnormalities in liver function tests observed with sulindac characteristically have reverted to normal after discontinuation of therapy.

Ocular Effects

Adverse ophthalmological effects have been observed with non-steroidal anti-inflammatory agents; accordingly, patients who develop visual disturbances during treatment with Aclin should have an ophthalmological examination.

Use in Pregnancy (Category C)

Australian Pregnancy Categorisation Definition of Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Aclin should not be given to pregnant women since safety for its use has not been established.

Non-steroidal anti-inflammatory drugs have an inhibitory effect on prostaglandin synthesis and, when given during the third trimester of pregnancy, may cause closure of the foetal ductus arteriosus, tricuspid incompetence and pulmonary hypertension, non-closure of ductus arteriosus postnatally which may be resistant to medical management, myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding or perforation, increased risk of necrotising enterocolitis, and delayed labour and birth.

Use in Lactation

Aclin should not be given to nursing mothers since safety for its use has not been established.

Paediatric Use

Aclin should not be given to children.

Interactions with Other Medicines

DMSO (dimethyl sulfoxide) should not be used with sulindac. Concomitant administration has been reported to reduce 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 Aclin is administered concomitantly with methotrexate. NSAIDs have been reported to decrease the tubular secretion of methotrexate and potentiate the toxicity.

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

Oral Hypoglycaemic. Although sulindac and its sulfide metabolite are highly bound to protein, studies in which sulindac was given at a dose of 400 mg daily, have shown no proven interaction with oral hypoglycaemic agents. However, patients should be monitored carefully until it is certain that no change in their hypoglycaemic dosage is required.

Other NSAIDs. The concomitant use of Aclin with other NSAIDs is not recommended due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy.

Aspirin (Acetylsalicylic Acid). The concomitant administration of aspirin 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 aspirin did not have a favourable effect on the therapeutic response to sulindac, the combination is not recommended.

Dextropropoxyphene hydrochloride/Paracetamol. Neither dextropropoxyphene hydrochloride nor paracetamol had any effect on the plasma levels of sulindac or its sulfide metabolite.

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

Antacids. A single dose crossover study compared 100 mg sulindac with 100 mg of sulindac administered with an antacid (magnesium and aluminium hydroxides, in suspension, 30 mL). There was no significant difference in absorption as measured by the urinary recovery of sulindac.

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.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics. The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

ADVERSE EFFECTS

Sulindac is generally well tolerated. Those side effects experienced are usually mild and may often respond to a reduction in dosage.

The following adverse effects were reported in clinical trials or have been reported since the drug was marketed.

Gastrointestinal. The most frequent types of side effects occurring with sulindac are gastrointestinal; these include gastrointestinal pain, dyspepsia, nausea with or without vomiting, diarrhoea, constipation, flatulence, anorexia and gastrointestinal cramps.

Dermatological. Rash, pruritus.

Central Nervous System. Dizziness, headache, nervousness.

Special Senses. Tinnitus.

Miscellaneous. Oedema.

Adverse Effects Reported Less Frequently

The probability exists of a causal relationship between sulindac and these side effects.

Gastrointestinal. Stomatitis, gastritis or gastroenteritis. Peptic ulcer, colitis, gastrointestinal bleeding and GI perforations have been reported rarely. Fatalities have occurred. Liver function test abnormalities, jaundice (sometimes with fever), cholestasis, hepatitis, hepatic failure, pancreatitis, ageusia, glossitis and intestinal strictures (diaphragms). It has been reported that a probable sulindac metabolite has been found in biliary sludge in patients with symptoms of cholecystitis who underwent a cholecystectomy.

Dermatological. Sore or 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), hypertension, palpitation.

Haematological. Thrombocytopenia, ecchymosis, purpura, agranulocytosis, leucopenia, neutropenia, bone marrow depression (including aplastic anaemia), haemolytic anaemia, increased prothrombin time in patients on oral anticoagulants.

Genitourinary. Urine discolouration, dysuria, haematuria, proteinuria, crystalluria, renal impairment (including renal failure), interstitial nephritis, nephrotic syndrome, vaginal bleeding.

Nervous System. Vertigo, insomnia, somnolence, paraesthesiae, convulsions, syncope, depression, psychic disturbances including acute psychosis, aseptic meningitis, sweating, asthenia.

Metabolic. Hyperkalaemia.

Musculoskeletal. Muscle weakness.

Special Senses. Visual disturbances including blurred vision, decreased hearing, metallic or bitter taste.

Respiratory. Epistaxis

Hypersensitivity Reactions. Anaphylaxis and angioneurotic oedema. Bronchial spasm, dyspnoea, hypersensitivity vasculitis, hypersensitivity syndrome (see **Precautions**).

Causal Relationship Unknown

Other reactions have been reported in clinical trials or since the drug was marketed, but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Nervous System. Neuritis.

Miscellaneous. Gynaecomastia. Rare occurrences of fulminant necrotising fasciitis, particularly in association with Group A *β*-haemolytic *streptococcus*, has been described in persons treated with non-steroidal anti-inflammatory agents, sometimes with fatal outcome (see **Precautions**).

Cardiovascular. Arrhythmia.

Metabolic. Hyperglycaemia.

Special Senses. Disturbances of the retina and its vasculature.

DOSAGE AND ADMINISTRATION

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

Aclin should be administered once or twice a day with fluids or food. Dosage should be adjusted to the severity of the disease. If used once daily, the drug should be taken in the evening.

The usual daily dosage of Aclin is 400 mg per day. However, the dosage may be lowered depending on the response. Doses above 400 mg per day are not recommended.

In acute gouty arthritis, therapy for 7 days is usually adequate.

OVERDOSAGE

Symptoms

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.

Treatment

In the event of acute overdosage, the patient should be carefully observed and given symptomatic and supportive treatment.

Animal studies show that absorption is decreased by the prompt administration of activated charcoal, which should be given within 1 to 2 hours after ingestion.

Contact the Poisons Information Centre on 131126 for advice on management and treatment of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Aclin, 100 mg tablet: orange-yellow, marked "SD" breakline "100" on one side, "α" on the other; bottles 50's.

Aclin 200, 200 mg tablet: orange-yellow, marked "SD" breakline "200" on one side, "α" on the other; bottle 50's.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 22 August 2005.

Date of most recent amendment: 8 November 2011.