PRODUCT MONOGRAPH

[Pr]TEVA-SULINDAC

(Sulindac Tablets, USP)

150 mg and 200 mg

Anti-inflammatory - Analgesic

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NAME OF DRUG

[Pr]TEVA-SULINDAC
(Sulindac Tablets, USP)
150 mg and 200 mg

PHARMACOLOGICAL CLASSIFICATION

Anti-inflammatory - Analgesic

ACTION AND CLINICAL PHARMACOLOGY

TEVA-SULINDAC (sulindac) is a nonsteroidal anti-inflammatory indene derivative drug which possesses both analgesic and antipyretic activities. The therapeutic action of sulindac is not due to pituitary-adrenal stimulation, but its mode of action is not known. The sulfide metabolite may be involved in the anti-inflammatory action of sulindac by inhibiting prostaglandin synthesis.

In clinical studies, a daily dosage of sulindac ranging from 200 to 400 mg was shown to be similar in effectiveness to a daily dosage of acetylsalicylic acid ranging from 2400 to 4800 mg.

A minimum of approximately 88% of an oral dose of sulindac is absorbed in man. In the fasting state, peak plasma concentrations of the biologically active sulfide metabolite are attained in approximately two hours following administration, and in about four hours when sulindac is administered with food. The apparent terminal half-life of the active sulfide metabolite is approximately 16 hours.

In man, the primary route of excretion is via urine, as both sulindac and its sulfone metabolite (free and glucuronidated forms). Approximately 50% of the administered dose is excreted in the urine and approximately 25% is found in the feces. The sulfone metabolite accounts for the major portion of the administered dose of sulindac appearing in the urine with the sulfide metabolite accounting for less than 1%. Both the sulfone and sulfide metabolites are found in the feces.

The average fecal blood loss measured over a two-week period in healthy men was statistically significantly less during administration of 400 mg per day of sulindac compared to 4800 mg per day of acetylsalicylic acid.

A comparative two-way, single-dose bioavailability study was performed on TEVA-SULINDAC 200 mg Tablets and Clinoril® 200 mg Tablets. The pharmacokinetic data calculated for the parent compound and two metabolites of the TEVA-SULINDAC and Clinoril® tablet formulations is tabulated below:

	AUC (mcg-hours/mL)	Cmax (mcg/mL)	Tmax (Hours)
Parent Compound			
TEVA-SULINDAC	16.79 ± 5.42	5.58 ± 2.45	3.06 ± 1.63
Clinoril®	16.30 ± 5.78	5.35 ± 2.20	3.13 ± 1.74
Sulfone Metabolite			
TEVA-SULINDAC	25.71 ± 9.98	2.05 ± 0.76	4.12 ± 1.50
Clinoril®	27.35 ± 7.33	2.29 ± 0.80	4.21 ± 1.29
Sulfone Metabolite			
TEVA-SULINDAC	22.44 ± 9.36	3.19 ± 1.30	4.48 ± 2.13
Clinoril®	22.72 ± 10.24	3.31 ± 1.32	4.19 ± 2.08

INDICATIONS AND CLINICAL USE

TEVA-SULINDAC (sulindac) is indicated for the relief of signs and symptoms related to osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute painful shoulder (acute subacromial bursitis/supraspinatus tendinitis) and acute gouty arthritis.

CONTRAINDICATIONS

1. Peptic ulcer or active inflammatory disease of the gastrointestinal system.

2. Known or suspected hypersensitivity to the drug. TEVA-SULINDAC (sulindac) should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

3. TEVA-SULINDAC should not be used in pediatric patients, pregnant women and nursing mothers because its safety in such patients has not been established. Sulindac has been shown to inhibit prostaglandin synthesis and release, an action which has been associated with an increased incidence of dystocia and delayed parturition in pregnant animals, when nonsteroidal anti-inflammatory drugs were administered late in pregnancy (see WARNINGS).

WARNINGS

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAID's) including sulindac.

TEVA-SULINDAC (sulindac) should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including TEVA-SULINDAC should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See PRECAUTIONS for further advice.

Use in Pregnant or Lactating Women:

The safety of sulindac has not been established in pregnant women and therefore the use of TEVA-SULINDAC is not recommended during pregnancy. Reproduction studies in the rat showed a decrease in average fetal weight and an increase in numbers of dead pups on the first day of the postpartum period at daily dosage levels of 20 and 40 mg/kg (2.5 and 5.0 times the usual maximum daily dose in humans), while there was no adverse effect observed on the survival and growth during the remainder of the postpartum period.

Sulindac prolongs the duration of gestation in rats, as do other compounds of this class which also may cause dystocia and delayed parturition in pregnant animals. Visceral and skeletal malformations were observed in low incidence among rabbits in some teratology studies but did not occur at the same dosage levels in repeat studies, nor at a higher dosage level in the same species. Although it is not known whether sulindac is secreted in human milk, nursing should not be undertaken while a patient is on TEVA-SULINDAC since it is known that sulindac is secreted in the milk of lactating rats.

PRECAUTIONS

Gastrointestinal System:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs TEVA-SULINDAC (sulindac) should be discontinued, an appropriate treatment instituted and the patient, closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of TEVA-SULINDAC therapy when and if these adverse reactions appear.

Renal Function:

As with other nonsteroidal 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 hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the 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 nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation.
Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

TEVA-SULINDAC and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of TEVA-SULINDAC should be anticipated and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Hepatic Function:

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued 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 with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if

systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Circulating levels of the sulfide and sulfone metabolites may be delayed, elevated and prolonged in patients with poor liver function. Such patients should be closely monitored and may require a reduction of daily dosage.

Pancreatic Function:

There have been several reported cases of pancreatitis in patients receiving sulindac and if this occurs, TEVA-SULINDAC treatment should be discontinued and should not be reinstituted (see ADVERSE REACTIONS).

Fluid and Electrolyte Balance:

Fluid retention and edema have been observed in patients treated with sulindac. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be born in mind. TEVA-SULINDAC should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

Hematology:

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when TEVA-SULINDAC is administered.

Sulindac has been shown to prolong bleeding time (but within normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, sulindac should be used with caution in patients with intrinsic coagulation defects and those on anticoagulant therapy.

Blood dyscrasias associated with the use of nonsteroidal anti-inflammatory drugs are rare, but could be with severe consequences.

Infection:

In common with other anti-inflammatory drugs, TEVA-SULINDAC may mask the usual signs of infection.

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of sulindac and other nonsteroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed: ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Central Nervous System:

Aseptic meningitis has been reported in connection with sulindac therapy in patients with systemic lupus erythematosus. Such patients may also develop hypersensitivity reactions to sulindac, such as fever, rash or abnormal function, more often than those with other disorders. Caution should therefore be exercised when considering sulindac therapy for patients with systemic lupus erythematosus.

Hypersensitivity Reactions:

Hive like swellings on the face, eyelids, mouth, lips or tongue, shortness of breath, troubled breathing, wheezing or tightness in the chest may occur with the use of TEVA-SULINDAC. If such symptoms develop this drug should be discontinued.

Use in Children:

Until further information is available TEVA-SULINDAC should not be used in children under 12.

Information for Patients:

When TEVA-SULINDAC is added to the treatment program of patients who have been on prolonged corticosteroid therapy and a decision is made to reduce or discontinue this treatment, this should be done gradually to avoid exacerbation of disease or adrenal insufficiency. Patients receiving sulindac should be instructed to report to their physicians any gastrointestinal manifestation, ocular symptoms, skin rash, weight gain or edema.

Drug Interactions:

Acetylsalicylic acid (ASA):

Animal studies indicated that acetylsalicylic acid administered with nonsteroidal anti-inflammatory drugs, including sulindac, produces a net decrease in anti-inflammatory activity with lowered blood levels of the non-acetylsalicylic acid drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of acetylsalicylic acid on sulindac blood levels. Correlative clinical studies have not been performed.

Anticoagulants:

Several short-term controlled studies failed to show that sulindac affects significantly prothrombin time or a variety of other clotting factors when administered to patients on coumarin type anticoagulants. However, bleeding has been reported when sulindac and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin type anticoagulants and therefore, TEVA-SULINDAC should be used cautiously in such cases.

DMSO:

DMSO should not be used with sulindac. Concomitant administration has been reported to reduce the plasma levels of the active sulfide metabolite and potentially reduce efficacy. In addition, this combination has been reported to cause peripheral neuropathy.

Diuretics:

Since sulindac may cause fluid retention, diuretic dose may need to be increased or sulindac therapy discontinued. The pharmacologic effect of loop diuretics (e.g. furosemide) may be decreased.

Lithium:

During concomitant administration, monitoring and reduction of lithium dose may be required since there is the possibility of decreased renal clearance and elevated levels of lithium.

Probenecid:

Concomitant administration of probenecid with sulindac increased plasma levels of sulindac and sulfone while having only a slight effect on plasma sulfide levels. Sulindac produced a modest reduction in the uricosuric action of probenecid, which, under most circumstances is not significant.

ADVERSE REACTIONS

Multiclinic, multi-investigator clinical trials involving 24,000 general practice patients with rheumatoid arthritis, osteoarthrosis or ankylosing spondylitis treated with sulindac

indicated the following adverse reactions and their approximate incidence (%). Additional adverse reactions were reported in additional clinical trials.

Gastrointestinal:

Gastrointestinal pain was the most common adverse reaction reported (7.2%). Other gastrointestinal disturbances included nausea, with or without vomiting (6.5%), constipation (3.0%), diarrhea (1.5%), dyspepsia, flatulence, anorexia and gastrointestinal cramps. The following adverse reactions had a frequency of less than 1%; gastritis or gastroenteritis, peptic ulcer, gastrointestinal bleeding, pancreatitis and gastrointestinal perforation which has been reported rarely.

Hepatobiliary:

Hepatobiliary effects were reported by less than 1% of the patients and included liver function abnormalities, jaundice, sometimes with fever, cholestasis and hepatitis.
Central Nervous System:

Central nervous system effects reported included dizziness (2.7%), drowsiness (2.1%), headache (1.7%). nervousness and tinnitus. CNS side effects reported less frequently (< 1%) included vertigo, somnolence, insomnia, sweating, asthenia and blurred vision.

Dermatologic:

Rash (3%) and pruritus were the most frequently reported dermatologic side effects, stomatitis, sore or dry mucous membranes, erythema multiforme, alopecia, photosensitivity, exfoliative dermatitis, toxic epidermal necrolysis and Stevens-Johnson syndrome were reported less frequently (< 1%).

Cardiovascular:

Congestive heart failure in patients with marginal cardiac function and palpitations are two cardiovascular side effects reported less frequently (< 1%).

Hematologic:

Hematologic effects with an incidence of less than 1% included, thrombocytopenia, ecchymosis, purpura, leukopenia and increased prothrombin time in patients on oral anticoagulants (see PRECAUTIONS).

Miscellaneous:

Edema has been reported in some patients (see PRECAUTIONS).

Hypersensitivity reactions including anaphylaxis and angioneurotic edema have been reported (< 1%). A potentially fatal apparent hypersensitivity syndrome has been reported

in a few patients which has consisted of some or all of the following findings: fever, chills, skin rash or other dermatologic reactions, changes in liver function, jaundice, pneumonitis, leukopenia, eosinophilia and renal impairment.

Other adverse experiences have been reported in patients receiving sulindac and although a casual relationship has not been established, the possibility cannot be excluded and the serious nature of some of these reactions requires that patients be monitored carefully by their physicians.

Cardiovascular:	hypertension
Hematologic:	bone marrow depression, including aplastic anemia and hemolytic anemia.
Nervous System:	paresthesias, neuritis
Special Senses:	transient visual disturbances, decreased hearing
Respiratory:	epistaxis
Psychiatric:	depression. psychic disturbances including acute psychosis
Genitourinary:	vaginal bleeding, hematuria, renal impairment, interstitial nephritis, nephrotic syndrome

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been reports of cases of overdosage and rarely deaths have occurred. Following overdosage, the following signs and symptoms may be observed: stupor, coma, diminished urine output and hypotension.

In acute sulindac overdosage, the stomach should be emptied immediately by emesis or by gastric lavage. Supportive and symptomatic treatment should be initiated and patients should be carefully monitored.

Animal studies have shown that absorption of sulindac from the GI tract is decreased by prompt administration of activated charcoal and elimination is enhanced by alkalinization of the urine.

DOSAGE AND ADMINISTRATION

TEVA-SULINDAC (sulindac) should be administered orally twice a day with food. The maximum recommended dose is 400 mg per day.

In osteoarthritis, rheumatoid arthritis and ankylosing spondylitis the recommended starting dosage is 150 mg twice a day. The dosage may be lowered or raised depending on the response.

In acute painful shoulder (acute subacromial bursitis/supraspinatus tendinitis) and acute gouty arthritis, the recommended dosage is 200 mg twice a day. After a satisfactory response has been achieved, the dosage may be reduced according to the response. In acute painful shoulder, therapy for 7 to 14 days is usually adequate. In acute gouty arthritis, therapy for 7 days is usually adequate.

AVAILABILITY

TEVA-SULIDAC 150mg:
Each yellow coloured, hexagonal shaped, bi-convex, compressed tablets; on one side stylized N engraved between broken vertical scoreline, 150 engraved on the reverse contains sulindac 150 mg.

TEVA-SULINDAC 200mg:
Each yellow coloured, hexagonal shaped, bi-convex, compressed tablets; on one side stylized N engraved between broken vertical scoreline, 200 engraved on the reverse contains sulindac 200 mg.

Supplied in bottles of 100, 500 and 1000 tablets.

PATIENT INFORMATION LEAFLET

PrTEVA-SULINDAC

(Sulindac Tablets, USP)
150 mg and 200 mg

Sulindac, which has been prescribed to you by your doctor, is one of a large group of nonsteroidal anti-inflammatory drugs (NSAID's) and is used to treat the symptoms of certain types of arthritis (rheumatism). It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

You should take sulindac only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

Be sure to take sulindac regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

This medicine is available only with your doctor's prescription. Remember:

- This medicine has been prescribed for your current medical problem only. It must not be given to other people or used for other problems unless you are otherwise directed by your doctor.

PROPER USE OF THIS MEDICINE

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking sulindac unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

SIDE EFFECTS OF THIS MEDICINE

Along with its beneficial effects, sulindac, like other NSAID drugs, may cause some undesirable reactions. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your doctor immediately if any of the following are noted:

- Bloody or black tarry stools
- Shortness of breath, wheezing, any trouble in breathing or tightness in the chest
- Skin rash, swelling, hives or itching
- Indigestion, nausea, vomiting, stomach pain or diarrhea
- Yellow discolouration of the skin or eyes, with or without fatigue
- Any changes in the amount or colour of your urine (such as dark; red or brown)
- Swelling of the feet or lower legs
- Blurred vision or any visual disturbance
- Mental confusion, depression, dizziness, lightheadedness
- Hearing problems

ALWAYS REMEMBER

Before taking this medication tell your doctor and pharmacists if you:

- are allergic to sulindac or other related medicines of the NSAID group such as acetylsalicylic acid, diflunisal, fenoprofen, flurbiprofen, diclofenac, indomethacin, ketoprofen, mefenamic acid, piroxicam, ibuprofen, tiaprofenic acid or tolmetin
- have a history of stomach upset, ulcers, or liver or kidney disease
- are pregnant or intend to become pregnant while taking this medication
- are breast feeding
- are taking any other medication (either prescription or nonprescription)
- have any other medical problem(s)
-

While taking this medication:

- Tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication.
- Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication. Tranquilizers, sleeping pills and certain antihistamines (anti-allergic) may increase the frequency and/or severity of these side effects.
- Check with your doctor if you are not getting any relief or if any problems develop.
- Report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.

- Your regular medical checkups are essential.
- If you want more information about this medicine, ask your doctor or pharmacist.

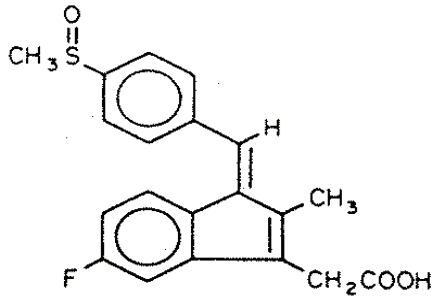
Teva Canada Limited
Toronto, Canada.

PHARMACEUTICAL INFORMATION

Trade Name: TEVA-SULINDAC

Proper Name: Sulindac

Structural Formula and Chemistry:
Sulindac is a nonsteroidal anti-inflammatory indene derivative. It is a member of the arylacetic class of nonsteroidal anti-inflammatory agents, such as indomethacin. Its chemical name is (Z)-5-f1uoro-2-methyl-1-{[p-(methylsulfinyl)phenyl]methylene)-1H-indene-3-acetic acid and it has the following structural formula:



Molecular Formula: $C_{20}H_{17}F0_3S$ Molecular Weight: 356.4

PHARMACOLOGY

Animal Pharmacology:

Sulindac possesses anti-inflammatory, antipyretic and analgesic activity. It was found to be more active than acetylsalicylic acid and half as potent as indomethacin in reducing carrageenan-induced swelling of the rat paw.

Relatively large doses of sulindac were required to inhibit urate induced inflammation of the dog knee joint. Sulindac showed moderate activity on topical application to the mouse ear against croton oil induced inflammation. Adjuvant induced arthritis in the rat and cotton pellet granuloma in the same species was significantly reduced with daily oral administration of sulindac. The analgesic and antipyretic activity of sulindac in the rat was equipotent to indomethacin. The anti-inflammatory activity of sulindac was reduced with prior treatment of low doses of acetylsalicylic acid.

At effective anti-inflammatory doses in the rat, sulindac was less active in producing gastrointestinal hemmorhage or perforation than indomethacin. In the guinea pig sulindac prevented aggregation of platelets following oral administration. Sulindac showed little central nervous system effects, uricosuric or diuretic activity, or cardiovascular or

respiratory effects. Mice infected with C. kutsheri showed no host resistance depression, however, hydrocortisone depressed host resistance in this same biologic system.

The physiologic disposition and metabolism of sulindac was studied in the dog, rat, rhesus monkey, and man. The drug was well absorbed in all species and excreted primarily in the urine of monkeys and humans.

The principal metabolites in all species were the sulfide and sulfone metabolites obtained through reduction (reversible) or oxidation (irreversible) of the sulfur atom of sulindac. Sulindac and its sulfone metabolite, both unchanged and as the conjugated glucuronide were the major metabolites in the urine. The sulfide metabolite, if present at all, was found in very low concentrations in the urine. Sulindac was extensively bound to human and animal plasma and was secreted in rat milk. Placental transfer occurred in the rat.

Sulindac and its two metabolites undergo extensive enterohepatic circulation in animals. Similar enterohepatic circulation together with the reversible metabolism are probably major contributors to sustained plasma levels of the active drug in man.

The sulfide metabolite given orally was much more active in anti-inflammatory tests than sulindac itself. When administered locally into the knee joint of dogs, the sulfide metabolite was considerably more active than sulindac itself in preventing urate-induced inflammation. The sulfide metabolite, but not sulindac, exhibited substantial activity in inhibiting aggregation of platelets in vitro. Sulindac was much less active than the sulfide metabolite in an in vitro system measuring prostaglandin synthetase activity. These data indicate that the sulfide metabolite accounts for most of the pharmacological activity of sulindac. The sulfone metabolite, on the other hand, had negligible pharmacologic activity.

TOXICOLOGY

Acute Toxicity:

Oral LD_{50} mg/kg (95% Confidence Limits):

Mice: 450 (300-675)

Rats: 225 (164-308)

Toxic effects observed in mice and rats included apathy, ptosis, depression, piloerection, urinary stain and rapid respiration. Severe growth suppression was noted in animals at all dose levels. Gross necropsy findings in the mice which died were slight hemorrhaging of the G.I. tract, slightly congested lungs, stomach wall distended with yellowish fluid and slightly congested adrenals. Gross necropsy findings in the rats which died included external evidence of urinary stain and occasional blood stains around the mouth and *eye.*

Internal evidence of gastritis, enteritis, congestion of the lungs and of the adrenal glands was observed.

The oral LD_{50} in dogs has been reported to be greater than 1600 mg/kg.

Subacute and Chronic Toxicity:

1. Rats:

(a) 4 weeks at dose levels of 5, 10, 20, 40 or 80 mg/kg/day. Chromorhinorrhea, pale extremities and micturition occurred throughout the study (primarily at 80 mg/kg/day); these signs also preceded death in 11 rats receiving 80 mg/kg/day. Flaccidity and abdominal distention occurred occasionally.

Drug related hematologic changes occurred at the high dose level and were found predominantly in female rats. Changes included: decreased hemoglobin concentration and hematocrit, marked increases in white blood cell counts and percent of neutrophils and monocytes, and a marked decrease in percent of lymphocytes. Several rats in the high dose group also developed nucleated red blood cells, anisocytosis, poikilocytosis, polychromasia, hypochromasia and hyperlobulated white blood cells.

Gross examination revealed drug induced ulcerative enteritis, ulcerative gastritis, fibrinopurulent peritonitis, and renal papillary necrosis at autopsy, mostly in the 80 mg/kg/day group.

(b) Two studies of 13 weeks at dose levels of 10, 20 or 40 mg/kg/day. No adverse physical signs attributable to treatment were seen in either study.

Hematological changes observed during treatment in the highest dose group consisted of a decrease in hemoglobin concentration and hematocrit accompanied, in some instances, by neutrophilia, lymphocytopenia and elevated erythrocyte sedimentation rate. Several rats in the first study also developed anisocytosis, poikilocytosis, polychromasia and hypochromia. A significant increase in glutamic pyruvic transaminase (GPT) occurred in female rats throughout the second study.

In the first study, changes seen at autopsy in rats given 40 mg/kg/day consisted of slight ulcerative enteritis and small gastric erosions in the fundic mucosa, renal papillary necrosis and papillary edema, and moderate thymic atrophy. Postmortem examination revealed gastric lesions in the second study, particularly in the high dose group, including superficial erosion, atrophy and ulceration of the gastric mucosa.

One female rat in the first study died of ulcerative enteritis and peritonitis after 81 doses (40 mg/kg/day). One male rat in the second study developed an ulcer.

(c) 53 weeks at dose levels of 5, 10 or 20 mg/kg/day orally. The principal changes observed were ulceration of the mucosa, or inflammatory nodules in the small intestine secondary to mucosal ulcers. Several rats in the 20 mg/kg/day group exhibited mild anemia, weight loss and neutrophilic leukocytosis secondary to the intestinal lesions. One rat in this dose group developed a gastric ulcer and another had renal papillary necrosis at the end of the study. The only other treatment related changes were slight increases in weight of the liver, kidneys, and spleen of male rats, and increased hemopoietic activity in the spleen in two rats with intestinal lesions. All of these changes occurred with the 20 mg/kg/day regimen.

(d) 105 weeks at dose levels of 5, 10 or 20 mg/kg/day. No treatment related physical signs were noted in this study.

2. Mice:

(a) 36 days oral dosing at 20, 40, 80 or 100 mg/kg/day.
No drug related physical signs were noted in the 20 mg/kg/day group. Signs of toxicity at 40, 80 and 100 mg/kg/day included pale extremities, unkempt coat, distended abdomen, weight loss and death; the incidence and severity of these signs were dose related.

The primary change noted at autopsy was gastrointestinal ulceration (40, 80 and 100 mg/kg/day). Renal changes included diffuse degenerative nephropathy (2 of 10 mice, 40 mg/kg/day), cortical tubular necrosis (1 of 10 mice, 80 mg/kg/day), cortical tubular vacuolation (4 of 10 mice, 20, 40 and 100 mg/kg/day) and papillary necrosis (2 of 10 mice, 40 and 100 mg/kg/day).

(b) 81 weeks oral dosing at 5, 10 or 20 mg/kg/day.
In the 20 mg/kg/day group, male mice lost weight during weeks 24 and 25; some also developed pale extremities during this time and died from gastrointestinal ulceration. From week 26 until the end of the study, no drug related physical changes occurred in the 20 mg/kg/day group and body weights remained similar to controls.

After 81 weeks of treatment, one mouse from the 10 mg/kg/day group developed a colonic ulcer. No gastrointestinal lesions were seen with doses of 5 mg/kg/day.

Both treated and control mice developed renal papillary necrosis; though the incidence was greater in treated mice, this was not considered drug related.

3. Dog:

(a) 13 days oral dosing at 80 to 320 mg/kg/day administered to 12 dogs.
Dose related emesis and soft bloody stools were observed during treatment. Yellow particles were frequently observed in the feces of dogs receiving 160 or 320 mg/kg/day and minor weight loss occurred in all dosage groups.

Slight to marked elevations in leukocyte counts were noted in dogs in the high and middle dose groups. In the high dose group, this was accompanied by relative neutrophilia and lymphocytopenia, and/or an increase in erythrocyte sedimentation rate. Drug related hepatic changes included: trace or small amounts of fat in the periportal liver cells, moderate bile duct proliferation, periductal fibrosis and elevations in SGOT and alkaline phosphatase activity. Numerous yellow crystals were observed in the bile from the gallbladder in all dosage groups.

One dog receiving 320 mg/kg/day developed slight or moderate acute arteritis in the thymus and spleen, inflammatory and necrotic lesions in lymphoid tissue, slight vasculitis in the liver and a small gastric ulcer accompanied by inflammation and necrosis.

No drug related changes in food consumption, ophthalmologic examinations, electrocardiograms or urinalyses were noted.

Drug administration was discontinued and the animals were held for 38 days without treatment. Signs of drug effect (emesis, leukocytosis, biochemical and histologic changes) completely disappeared during the recovery period.

(b) 14 weeks oral dosing at 5, to, 20 or 40 mg/kg/day.
Dose related physical signs included soft stools, diarrhea and emesis.

No significant changes attributable to drug treatment were noted in: ophthalmologic examination, electrocardiograms, body weight, food consumption, water intake or urinary output measurements, or hematologic or urologic studies.

At autopsy, yellow crystals were present in the gallbladder of all dogs in the 40 mg/kg/day group, but no pathologic changes were evident in the gallbladder. Two dogs (20 and 40 mg/kg/day) showed an increase in kidney weight; liver weight also increased and was associated with slight cytoplasmic rarefaction of the periportal liver cells.

(c) 6 weeks at a dose level of 40 mg/kg/day.
No drug related ophthalmologic, hematologic or biochemical changes were noted. Physical appearance and body weight were also unchanged as well as gross or microscopic postmortem examinations.

(d) 53 weeks oral dosing at 5, 10 or 20 mg/kg/day.
This study produced no changes in physical signs attributable to sulindac. No drug related changes were seen in ophthalmologic examinations, electrocardiograms, urinalyses and hematologic and biochemical studies. At the end of the treatment period, liver changes consisting of slight mononuclear cell infiltration, bile duct proliferation, periportal fibrosis, cytoplasmic vacuolation and lipid deposition were observed in 4 of 6 dogs receiving 20 mg/kg/day.

4. Monkeys:

(a) 87 or 88 consecutive days oral dosing at 5, 10, 20, 40 or 80 mg/kg/day administered to male and female monkeys.

No treatment related antemortem or postmortem changes were noted in monkeys given 5 or 10 mg/kg/day. No significant ophthalmologic alterations or changes in body and organ weight could be attributed to treatment with sulindac at any dose level.

During the first week of treatment one monkey given 80 mg/kg/day developed anorexia and emesis was noted in two monkeys (40 and 80 mg/kg/day). Yellow crystalline particles similar in appearance to sulindac were present in the feces of two monkeys (20 and 80 mg/kg/day). Microscopic examination of urine sediment of two monkeys (40 and 80 mg/kg/day) showed numerous sheaths of linear yellow crystals.

Hematologic changes associated with sulindac included an increase in erythrocyte sedimentation rate and total leukocytes in one monkey at 80 mg/kg/day. Drug related hematologic changes did not occur at any other dose level.

Serum biochemical changes included: increased serum bilirubin in monkeys at 80 mg/kg/day; increased SGOT activity at 20, 40 or 80 mg/kg/day; increased serum alkaline phosphatase activity at 40 or 80 mg/kg/day; increased serum creatinine concentration at 40 or 80 mg/kg/day; and an upward trend in blood urea nitrogen in monkeys at 80 mg/kg/day.

Morphologic changes due to treatment included an increased incidence and amount of focal interstitial nephritis in 4 monkeys receiving 80 mg/kg/day. Similar changes of lesser degree were observed in 2 monkeys from the 40 mg/kg/day treatment group and could not be dissociated from treatment though similar lesions occurred in 2 control monkeys. Hepatic changes in monkeys receiving 40 and 80 mg/kg/day included a slight or moderate portal fibrosis, bile duct proliferation, mixed periportal inflammatory cell infiltration and slight or moderate rarefaction of centrilobular hepatocytes. Yellow crystals were present in the gallbladder and intrahepatic bile ducts of one monkey at 40 mg/kg/day. A small amount of focal hepatocytic necrosis was noted in one monkey at 80 mg/kg/day. No morphologic changes related to treatment were observed at dosage levels of 5, 10, or 20 mg/kg/day.

Reproduction Studies:

All three segments of the reproduction studies were performed. Fertility and general reproductive performance was determined in rats; teratogenicity was evaluated in mice, rabbits, and rats; perinatal/postnatal effects were studied in rats; a parturition study and a mutagenic study were done in mice.

Reproduction studies in the rat showed a decrease in average fetal weight and an increase in numbers of dead pups on the first day of the postpartum period at daily dosage levels of 20 and 40mg/kg (2.5 and 5.0 times the usual maximum daily dose in humans), while there was no adverse effect observed on the survival and growth during the remainder of the postpartum period. Sulindac was found to prolong the duration of gestation in rats, as do other compounds of this class. Visceral and skeletal malformations were observed in low incidence among rabbits in some teratology studies but did not occur at the same dosage levels in repeat studies, nor at a higher dosage level in the same species. It is known that sulindac is secreted in the milk of lactating rats. There was no reproductive performance disturbance in either male or female rats at a dose level up to 40 mg/kg/day.

Carcinogenicity Studies:

In the 81 week mouse study and the 105 week rat study, the incidences of neoplasia in the treated groups were the same as the controls.

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