

# DACLIN

Sulindac

100mg & 200mg Tablets

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## Presentation

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Daclin 100mg tablets: Yellow flat bevel edged, 5/16" diameter with a bisect on one side.

Daclin 200mg tablets: Yellow flat bevel edged, 7/16" diameter with a bisect on one side.

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## Uses

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### Actions

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

Prostaglandin synthetase inhibition has been hypothesised to be the basis of the mechanism of action of non-steroidal anti-inflammatory agents. 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.

### *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 aluminium 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 are 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 is found in the faeces, primarily as the sulfone and sulfide metabolites.

## Indications

DACLIN is indicated for acute or long-term use in the treatment of the following:

- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis
- Periarticular diseases such as acute painful shoulder (acute subacromial bursitis/supraspinatus tendonitis) and tenosynovitis
- Acute gouty arthritis
- Painful low back syndrome (low back pain, commonly referred to as lumbago).

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## Dosage and Administration

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

DACLIN is available for administration as yellow tablets containing 100 mg or 200 mg sulindac.

DACLIN should be administered twice a day. Dosage should be adjusted to the severity of the disease.

The usual daily dosage of DACLIN is 400 mg per day. However, the dosage may be lowered depending on the response. Dosages above 400 mg per day are not recommended (see Warnings and Precautions).

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

DACLIN when administered orally should be taken with fluids or food.

Caution must be taken with dosage in the elderly and in patients with liver and/or renal impairment.

The propensity of NSAIs to interact with other medicines may influence the treatment of other conditions.

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## Contraindications

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Hypersensitivity to any component of this product.

DACLIN should not be used in patients in whom acute asthmatic attacks, urticaria, or rhinitis have been precipitated by acetylsalicylic acid or other nonsteroidal anti-inflammatory agents.

The medicine should not be administered to patients with active gastrointestinal bleeding, active peptic ulcer, or a history of recurrent gastrointestinal ulceration or bleeding.

Since paediatric indications and dosage have not been established, DACLIN should not be given to children.

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## Warnings and Precautions

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Bronchospasm has been associated with NSAIDs including sulindac and these agents should be used with particular caution in asthmatics.

### 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 rarely 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 with for 3-6 months and in about 2-4% 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 ulceration occurs 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.

### 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.

## **Platelet Aggregation**

Sulindac has less effect on platelet function and bleeding time than acetylsalicylic acid; however, since sulindac is an inhibitor of platelet function, patients who may be adversely affected should be carefully observed when sulindac is administered.

## **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 reinstated.

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, leukopenia, leukocytosis, 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).

## **Infections**

Non-steroidal anti-inflammatory medicines, including sulindac, may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the medicine with extra care in the presence of existing infection.

## **Ocular Effects**

Because of reports of adverse eye findings with agents of this class it is recommended that patients who develop eye complaints during treatment with sulindac have ophthalmological evaluations.

## **Cardiovascular Effects**

Peripheral oedema has been observed in some patients taking sulindac. Therefore, as with other medicines in this class, sulindac should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposed to fluid retention.

## **Hepatic Effects**

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 daily dosage may be required. NSAIDs should be administered to patients with impaired liver function only in cases of necessity.

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 sulindac develops unexplained fever, rash or other dermatologic reactions or constitutional symptoms. In cases where this syndrome is suspected, therapy should be discontinued immediately, and not reinstated.

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

Significant (3 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 function test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy.

## **Renal Effects**

As with other non-steroidal anti-inflammatory agents, there have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving sulindac.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a non-steroidal anti-inflammatory agent may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotic medicine. A non-steroidal anti-inflammatory medicine should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

Since sulindac is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be used to avoid excessive medicine accumulation.

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

Patients on long term therapy should have blood chemistry and renal function checked periodically. Treatment should immediately be withdrawn if any impairment becomes evident. The propensity of NSAIs to interact with other medicines may influence the treatment of other conditions.

## **Use in Children**

See Contraindications.

## **Use in Pregnancy**

Sulindac should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the foetus.

The known effects of medicines in this class on the human foetus during the third trimester of pregnancy include: constriction of the ductus arteriosus prenatally, tricuspid incompetence, and pulmonary hypertension; non-closure of the 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 and increased risk of necrotizing enterocolitis. Use of sulindac during the third trimester of pregnancy is not recommended.

## **Use in Nursing Mothers**

It is not known whether sulindac is excreted in human milk. Because other medicines of this class are excreted in human milk, a decision should be made whether to discontinue nursing or discontinue the medicine, taking into account the importance of the medicine to the mother.

## Animal Toxicology

Toxicological studies on sulindac include acute toxicity in mice, rats and rabbits; reproduction studies in the rat; teratogenic studies in the mouse, rat and rabbit; 3-month oral toxicity in the rat and dog, 81 weeks in the mouse, and 2 years in the rat; and mutagenicity in the mouse.

After single acute oral doses, the LD50 values in female mice, female and male rats, and male and female rabbits were 575, 365, and 413 mg/kg, respectively. The compound was generally more toxic after intraperitoneal than oral administration. There were no sex differences and little species differences in acute toxicity.

In teratogenic studies in the mouse and rat, the highest dose level tested (60 mg/kg in the mouse and 40 mg/kg in the rat) resulted in reduced maternal weight gain and decreases in foetal body weight. There was, however, no evidence of embryotoxicity or teratogenicity at any dose tested (10 to 60 mg/kg in the mouse and 10 to 40 mg/kg in the rat).

In reproduction studies in the rat, a decrease in average foetal weight and an increase in numbers of dead pups was observed on the first day of the postpartum period at dosage levels of 20 and 40 mg/kg/day (2.5 and 5 times the usual maximum daily dose in humans), although there was no adverse effect on 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 observed in low incidence among rabbits in some teratology studies did not occur at the same dosage levels in repeat studies, nor at a higher dosage level in the same species.

Sulindac crosses the placental barrier in the rat to a minimal degree and was excreted to a minor extent in rat milk. The medicine had no mutagenic effect, as judged by the dominant lethal assay in the mouse, after administration of 5 or 15 mg/kg/day to male mice either as a single dose or for five consecutive days.

In chronic studies in mice, rats, and monkeys at high doses, there were occasional occurrences of mild renal toxicity as evidenced by papillary oedema or mild interstitial nephritis in some animals. Papillary necrosis occurred infrequently in mice and rats.

Toxicologic changes attributable to sulindac were not observed at an oral dosage level of 10 mg/kg/day for periods of up to 3 months in monkeys and approximately 6 months in dogs and rats, but treatment of rats for periods up to one year resulted in a low incidence of intestinal ulcers at 5 or 10 mg/kg/day. Dogs treated for one year at doses of 5 or 10 mg/kg/day did not exhibit lesions attributable to treatment, although 20 mg/kg/day for the same period caused minor hepatic changes. Other changes evident at 20 mg/kg/day were infrequent and included renal papillary oedema or renal papillary necrosis, each occurring in a single rat; increased kidney weight in 1 of 4 dogs; and a transient elevation of serum glutamic oxaloacetic transaminase activity in 1 of 4 monkeys. A low incidence of gastrointestinal ulcers also was observed in rats given 20 mg/kg/day for 27 weeks, but dogs given this dose for this period of time did not exhibit any anatomical change attributable to treatment.

Similar gastrointestinal ulceration and renal papillary oedema or necrosis have been observed in studies with acetylsalicylic acid in the rat and dog.

Toxic effects at high doses (40 or 80 mg/kg/day or more) were similar: renal papillary necrosis or oedema and gastrointestinal ulcers in the rat and dog; a low grade hepatopathy, increase in incidence of interstitial nephritis over that of controls in the monkey; and hepatic changes in the dog. At the very high doses of 80 to 320 mg/kg/day in the dog, anaemia and vascular lesions secondary to gastrointestinal lesions were also seen. Although these levels were evidently toxic, withholding treatment permitted recovery.

Gastrointestinal lesions and renal lesions including papillary necrosis and tubular necrosis or nephropathy occurred in mice given 40 to 100 mg/kg/day of sulindac for 36 days.

In an 81-week study of the carcinogenic potential of sulindac in mice at dose levels of 5 to 20 mg/kg/day the type and incidence of neoplasia was similar in all groups (including the controls) and was not affected by treatment.

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## **Adverse Effects**

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Sulindac is generally well-tolerated. If adverse effects are experienced, they 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 medicine was marketed.

### **Adverse Effects Reported Frequently**

#### ***Gastrointestinal***

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

#### ***Dermatologic***

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 adverse 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 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 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, palpitation, hypertension.

### ***Haematologic***

Thrombocytopenia, ecchymosis, purpura, leukopenia, agranulocytosis, neutropenia, bone marrow depression; including aplastic anaemia, haemolytic anaemia, increased prothrombin time in patients on oral anti-coagulants.

### ***Genitourinary***

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

### ***Nervous System***

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

### ***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 Warnings and Precautions).

## **Adverse Effects—Causal Relationship Unknown**

Other reactions have been reported in clinical trials or since the medicine was marketed, but occurred under circumstances where a casual 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.

### ***Cardiovascular***

Arrhythmia.

### ***Metabolic***

Hyperglycaemia.

### ***Nervous System***

Neuritis.

### ***Special Senses***

Disturbances of the retina and its vasculature.

## **Miscellaneous**

Gynecomastia. Rare occurrences of fulminant necrotizing fasciitis, particularly in association with Group A  $\beta$ -haemolytic streptococcus, has been described in persons treated with non-steroidal anti-inflammatory agents, sometimes with fatal outcome (see also Warnings and Precautions).

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## **Interactions**

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### **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 concomitantly with methotrexate. Non-steroidal anti-inflammatory medicines have been reported to decrease the tubular secretion of methotrexate and potentiate the toxicity.

### **Cyclosporine**

Administration of non-steroidal anti-inflammatory medicines concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, 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 adverse effects. Since the addition of acetylsalicylic acid did not have a favourable effect on the therapeutic response to sulindac, the combination is not recommended.

### **Other NSAIDs**

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

### **Oral Anticoagulants and Hypoglycaemic Agents**

Although sulindac and the sulfide metabolite are highly bound to protein, studies, in which sulindac was given at a dose of 400 mg daily, have shown 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.

An increased prothrombin time has been observed in patients taking oral anticoagulants with sulindac (see Adverse Effects Reported Less Frequently – Haematologic).

### **Diflunisal**

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.

### **Diuretics**

Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the effect of diuretics.

### **Antihypertensive Medications**

Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the effect of antihypertensive drugs. In some patients with compromised renal function, the co-administration of an NSAID and an ACE inhibitor or angiotensin II antagonist may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible.

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## Overdosage

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Cases of overdosage have been reported 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 alkalinisation of the urine.

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## Pharmaceutical Precautions

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Store below 25°C. Keep container tightly closed. Protect from sunlight and excessive heat.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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100 mg: Bottle packs of 100 and 500 (not currently marketed) tablets.

200 mg: Bottle packs of 100 and 500 (not currently marketed) tablets.

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## Further Information

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Nil.

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## Name and Address

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## Date of Preparation

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2 February 2009