PRODUCT MONOGRAPH

Rhodacine

Indomethacin suppositories USP

100 mg

Nonsteroidal anti-inflammatory analgesic agent

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Control #: 093319

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PHARMACEUTICAL / THERAPEUTIC CLASSIFICATION

Nonsteroidal anti-inflammatory analgesic agent

ACTION AND CLINICAL PHARMACOLOGY

Indomethacin is a nonsteroidal anti-inflammatory drug with marked analgesic, and antipyretic properties. It has a unique chemical structure, which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds and colchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function.

Indomethacin is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an *in vivo* effect as well.

Although indomethacin does not alter the course of the underlying disease, it has been found effective to relieve pain, reduce fever, swelling and tenderness, and increase

mobility in patients with rheumatic diseases, including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and gout.

Pharmacokinetics:

In man, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 μg/mL at approximately 2 hours following single oral doses of 25 and 50 mg, respectively. Ninety percent of the orally administered indomethacin is absorbed within 4 hours. The suppository formulation is more rapidly and completely absorbed than the oral dose of indomethacin. Thus, C_{max} after rectal administration is lower than after oral dosing. The mean half-life of indomethacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 or 50 mg t.i.d., the steady state plasma concentrations of indomethacin are on average 1.4 times those following the first dose.

Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60% of an oral dosage is recovered in urine as drug and metabolites (26% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin).

About 90 percent of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentration.

Comparative bioavailability of Rhodacine vs Indocid® 50 and 100 mg Indomethacin Suppositories:

A single dose comparative bioavailability study was conducted in order to evaluate the rate and extent of absorption of **Rhodacine** versus Indocid® 100 mg indomethacin suppositories. The study was conducted in 18 healthy adult male volunteers under fasting conditions; all subjects enrolled were able to complete the study. The results are summarized in Table 1.

TABLE 1 Summary Table of the Comparative Bioavailability Data of Rhodacine vs Indocid® 100 mg Indomethacin Suppositories

Geometric mean
Arithmetic mean (CV%)

Parameter	Rhodacine		Indocid®		Ratio of means (90% CIs)
AUC_t (µg.h/mL)	12.34 13.20	(34.5)	13.73 14.32	(27.1)	90.6 (80.4-102.1)
AUC_{inf} (µg.h/mL)	13.45 14.47	(35.2)	15.16 15.60	(26.1)	89.2 (77.2-103.2)
C_{max} (µg/mL)	2.85 2.95	(25.7)	2.79 2.89	(28.2)	101.9 (91.2-113.9)
T_{max} (h)	1.64	(0.48)	1.67	(0.51)	--
$T_{1/2}$ (h)	7.64	(4.51)	7.46	(4.66)	--

For the T_{max} and $T_{1/2}$ parameters the arithmetic means (and standard deviations) are indicated.

INDICATIONS AND CLINICAL USE

Rhodacine (indomethacin) is not a simple analgesic, and its use should be limited to the conditions listed below, particularly those cases not responding to conservative measures.

Indomethacin has been found effective in the symptomatic treatment of:

- Selected cases of rheumatoid arthritis;
- Ankylosing (rheumatoid) spondylitis;
- Gout;
- Selected cases of severe osteoarthritis, including degenerative disease of the hip.

In these conditions **Rhodacine** may on occasion replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds and colchicine.

Rhodacine suppositories are for those patients in whom rectal administration is preferred.

Rheumatoid arthritis:

Rhodacine may be used singly or in combination with other agents. However, it should not be used as a drug of first choice because of the adverse reactions that may occur with its use.

Best results (relief of pain, tenderness, swelling and stiffness) have been obtained in the acute episodes of the disease. However, in many patients with chronic rheumatoid arthritis, indomethacin will produce a significant lessening of pain and stiffness within 48 hours. In other patients, treatment must be continued longer before significant subjective relief or objective evidence of decreased joint swelling and tenderness occur. In some cases of chronic rheumatoid arthritis, it may be necessary to continue treatment for at least a month before concluding that it has not produced significant

benefit. Use of indomethacin may enable reduction of steroid dosage in patients receiving corticosteroids. In such instances, the steroid dosage should be reduced slowly.

Ankylosing (rheumatoid) spondylitis:

Indomethacin frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

Osteoarthritis:

Indomethacin should be used in those cases of severe osteoarthritis which do not respond to treatment with other drugs such as the salicylates. In many cases prompt relief of pain is obtained.

Degenerative joint disease (osteoarthritis) of the hip:

Indomethacin may be used to provide relief of pain and increased range of motion in patients with degenerative joint disease of the hip.

Gout:

In acute attacks of gout, the response to indomethacin is usually rapid and often dramatic. Marked reduction of pain may be obtained within 2 to 4 hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases over a 3 to 5 day period.

CONTRAINDICATIONS

The following are contraindications to the use of indomethacin:

1. Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

2. Known or suspected hypersensitivity to the drug or other nonsteroidal anti-inflammatory drugs. The potential for cross-reactivity between different NSAIDs must be kept in mind.
   Indomethacin should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

3. Significant hepatic impairment or active liver disease.

4. Severely impaired or deteriorating renal function [creatinine clearance <30 mL/min (0.5 mL/sec.)]. Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

5. Indomethacin is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

6. Indomethacin suppositories are contraindicated in subjects with a recent history of rectal bleeding or proctitis.

WARNINGS

Gastrointestinal system (GI):

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal can occur at any time, with or without symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) including indomethacin.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with nonsteroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases.

The incidence of these complications increases with increasing dose.

Rhodacine 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 such as ulcerative colitis and Crohn's disease. In these cases, the physician must weigh the benefits of treatment against the possible hazards.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their hemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, **Rhodacine** should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anti-coagulant use have been associated with increased risk.

Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

Use in the elderly:

Patients older than 65 years and fragile or debilitated patients are most susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAIDs); the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

Cross sensitivity:

Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may also be sensitive to any of the other NSAIDs.

Aseptic meningitis:

In occasional cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissues diseases, etc.) seem to be pre-disposed. Therefore, in such patients the physician must be vigilant to the development of this complication.

Use in pregnancy, labour and lactation:

The known effects of drugs of this class on the human fetus during the third trimester of pregnancy are closure of the ductus arteriosis, platelet dysfunction with resultant bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation and myocardial degenerative changes.

Administration of indomethacin is therefore not recommended during pregnancy or in nursing mothers.

Use in children:

The drug should not be prescribed for children as safe conditions for use have not been established. In a few cases of severe juvenile rheumatoid arthritis, where indomethacin was given along with other drugs, severe reactions, including fatalities, were reported.

Others:

Occupational hazards: Patients should be warned that they may experience dizziness and in this event should not operate motor vehicles and should avoid potentially dangerous activities which require alertness.

Indomethacin should be used with caution in patients with psychiatric disturbances, epilepsy, or parkinsonism, since it may, in some instances, aggravate these conditions.

PRECAUTIONS

Gastrointestinal system:

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 the continuation of indomethacin therapy when and if these adverse reactions appear.

Indomethacin, both capsules and suppositories, should be used with caution because of the gastrointestinal reactions which may occur. The gastrointestinal effects may be decreased by giving the oral formulations of the drug immediately after meals, with food or with antacids. The risk of continuing therapy with indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient. Indomethacin suppositories should be given with caution to patients with any anal or rectal pathology.

Studies in normal subjects with radioactive chromate-tagged red blood cells indicate that large doses of indomethacin (50 mg four times a day) produce less fecal blood loss than average doses of acetylsalicylic acid (600 mg 4 times a day). Indomethacin however may cause single or multiple ulceration of the stomach, duodenum, or small and large intestine. There have been reports of severe bleeding and cases of perforation, with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, the drug should be discontinued. In many patients with peptic ulceration, a history of a previous ulcer was present or they were on concomitant steroids, salicylates or phenylbutazone. A possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present. In some patients there was no history of a previous ulcer and other drug were not being given. As a result of obvious or occult gastrointestinal bleeding some patients may manifest anemia. For this reason appropriate blood determinations are recommended periodically.

Renal function:

Long term administration of nonsteroidal anti-inflammatory drugs 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 drugs 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.

Indomethacin 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, utilization of lower doses of indomethacin should be considered and patients carefully monitored.

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

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state (see Drug interactions).

Since indomethacin 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 drug accumulation.

Genitourinary tract:

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with indomethacin must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hepatic function:

As with other nonsteroidal anti-inflammatory drugs (NSAIDs), borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Significant (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients receiving therapy with nonsteroidal anti-inflammatory drugs. 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 reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with 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 there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Fluid and electrolyte balance:

Fluid retention and edema have been observed in patients treated with indomethacin. 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 borne in mind. Indomethacin should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with β-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Hematology:

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when indomethacin is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of nonsteroidal anti-inflammatory drugs are rare, but could occur with severe consequences.

Indomethacin, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with ASA and usually disappears within 24 hours after discontinuation of indomethacin. Indomethacin has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying hemostatic defects, indomethacin should be used with caution in persons with coagulation defects.

Infection:

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

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of indomethacin 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:

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of indomethacin. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Headaches may occur, usually early in treatment with indomethacin. If headaches persist despite dosage reduction, therapy with indomethacin should be discontinued (see Warnings).

Hypersensitivity reactions:

Patients should be followed carefully to detect unusual manifestations of drug sensitivity, and since advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly.

Drug interactions:

Acetylsalicylic acid (ASA) or other NSAIDs:

The use of indomethacin in addition to any other NSAID, including those over the counter ones (such as ASA and ibuprofen) is not recommended due to the possibility of additive side effects.

Controlled clinical studies have shown that the combined used of indomethacin and acetylsalicylic acid does not produce any greater therapeutic effect than the use of indomethacin alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of ASA/day decreases indomethacin blood levels approximately 20%.

Digoxin:

Indomethacin given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indomethacin and digoxin are used concomitantly, serum digoxin levels should be closely monitored.

Anticoagulants:

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding.

Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of indomethacin with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

Clinical studies have shown that indomethacin did not influence the hypoprothrombinemia produced by the use of anticoagulants in patients and in normal subjects. However, when any additional drug, including indomethacin is added to the treatment of patients on anticoagulant therapy, the patient should be observed closely for alterations of the prothrombin time.

Oral hypoglycemics:

Indomethacin and hypoglycemic agents should not be used concomitantly.

Diuretics:

In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when indomethacin and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Indomethacin reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

Indomethacin and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indomethacin.

Anti-hypertensives:

Co-administration of indomethacin and some anti-hypertensive agents has resulted in an attenuation of the latter's hypotensive effect acutely, due at least in part to indomethacin's inhibition of prostaglandin synthesis. Caution should be exercised when considering the addition of indomethacin to the regimen of a patient taking one of the following anti-hypertensive agents; an alpha-adrenergic blocking agent (such as prazosin), an angiotensin converting enzyme inhibitor (such as captopril or lisinopril), a beta-adrenergic blocking agent, a diuretic (see Diuretics), or hydralazine.

A decrease in the antihypertensive effect of beta-adrenergic receptor blocking agents by nonsteroidal anti-inflammatory drugs including indomethacin has been reported. Therefore, when using a beta blocking agent to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained.

Glucocorticoids:

Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Methotrexate:

Caution should be used if indomethacin is administered simultaneously with methotrexate. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Lithium:

Indomethacin 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis resulting in renal vasoconstriction and decreased lithium excretion. As a consequence, when indomethacin and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read the product monographs for the appropriate lithium preparation before use of such concomitant therapy). In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

Protein bound drugs:

Indomethacin is extensively (99%) protein bound to human serum albumin and may compete for binding sites with drugs such as sulfonamides, oral hypoglycemic agents,

phenytoin or lithium. Although no significant interaction has been documented, patients with such combination therapy should be monitored.

Platelet adhesion:

Indomethacin decreases platelet adhesion and aggregation. Therefore, it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

The following interactions have not been documented with every NSAID. However, they have been reported with several of these medications and should be considered potential precautions to the use of any NSAID, especially with chronic administration.

Acetaminophen:

Prolonged concurrent use of acetaminophen with an NSAID may increase the risk of adverse renal effects; it is recommended that patients be under close medical supervision while receiving such combined therapy.

Alcohol:

Concurrent use of alcohol with an NSAID may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage.

Colchicine:

Concurrent use of colchicine with an NSAID may increase the risk of gastrointestinal ulceration or hemorrhage. Inhibition of platelet aggregation by NSAIDs, added to colchicine's effects on blood clotting mechanisms, may increase the risk of bleeding at sites other than the gastrointestinal tract.

Oral antidiabetic agents:

NSAIDs may increase the hypoglycemic effect of oral antidiabetic agents because prostaglandins are directly involved in regulatory mechanisms of glucose metabolism

and possibly because of displacement of the oral antidiabetic from serum proteins. Dosage adjustments of the antidiabetic agent may be necessary.

Potassium supplements:

Concurrent use of potassium supplements may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage.

Valproic acid:

Valproic acid may cause hypoprothrombinemia. In addition, it may inhibit platelet aggregation. Concurrent use with an NSAID may increase the risk of bleeding because of additive interference with platelet function and the potential occurrence of NSAID-induced gastrointestinal ulceration or hemorrhage.

Other Drugs Interactions:

Cyclosporine:

Administration of nonsteroidal anti-inflammatory drugs 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.

Diflunisal:

The combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. The co-administration of diflunisal and indomethacin results in an increase of about 30 to 35% in indomethacin plasma levels and a concomitant decrease in renal clearance of indomethacin and its conjugate. Therefore, indomethacin and diflunisal should not be used concomitantly.

Probenecid:

When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of

indomethacin may produce a therapeutic effect. When increases in the dose of indomethacin are made under these circumstances, they should be made cautiously and in small increments.

Phenylpropanolamine:

Hypertensive crises have been reported due to oral phenylpropanolamine alone and rarely to phenylpropanolamine given with indomethacin. This additive effect is probably due at least in part to indomethacin's inhibition of prostaglandin synthesis. Caution should be exercised when indomethacin and phenylpropanolamine are administered concomitantly.

Clinical laboratory tests:

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

ADVERSE REACTIONS

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly.

The following adverse reactions for capsules have been arranged into 2 groups: **(1)** incidence greater than 1%; and **(2)** incidence less than 1%. The incidence for group **(1)** was obtained from 33 double-blind controlled clinical trials reported in the literature (1092 patients). The incidence for group **(2)** was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely.

In control clinical trials, the incidence of adverse reactions to indomethacin SR capsule and equal 24-hour doses of indomethacin capsules were similar.

The adverse reactions reported with indomethacin capsules may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the suppositories.

Gastrointestinal: Incidence >1%: Nausea* with or without vomiting; dyspepsia* (including indigestion, heartburn and epigastric pain); diarrhea; abdominal distress or pain; constipation.

Incidence < 1%: Anorexia; bloating (includes distension); flatulence; peptic ulcer; gastroenteritis; rectal bleeding; proctitis; single and multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines; intestinal ulceration associated with stenosis and obstruction; gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.); development of ulcerative colitis and regional ileitis; ulcerative stomatitis; toxic hepatitis and jaundice (some fatal cases have been reported).

Central nervous system: Incidence >1%: Headache; dizziness*; vertigo; somnolence; depression and fatigue (including malaise and listlessness).

Incidence < 1%: Anxiety (includes nervousness); muscle weakness; involuntary muscle movements; insomnia; muzziness; psychic disturbances including psychotic episode; mental confusion; drowsiness, lightheadedness; syncope; paresthesia; aggravation of epilepsy and parkinsonism; depersonalization; coma; peripheral neuropathy; convulsions; dysarthria.

Dermatologic: Incidence >1%: None.

Incidence <1%: Pruritus; rash; urticaria; petechiae or ecchymosis; exfoliative dermatitis; erythema nodosum; loss of hair; Stevens-Johnson syndrome; erythema multiforme; toxic epidermal necrolysis.

Cardiovascular: Incidence >1%: None.

Incidence <1%: Hypertension; hypotension; tachycardia; chest pain; congestive heart failure; arrhythmia; palpitations.

Special Senses: Incidence >1%: Tinnitus.

Incidence <1%: Ocular-corneal deposits and retinal disturbances including those of the macula, have been reported in some patients on prolonged therapy with indomethacin; blurred vision, diplopia; hearing disturbances, deafness.

Hematologic: Incidence >1%: None.

Incidence <1%: Leukopenia; bone marrow depression; anemia secondary to obvious or occult gastrointestinal bleeding; aplastic anemia; hemolytic anemia; agranulocytosis; thrombocytopenic purpura; disseminated intravascular coagulation.

Genitourinary: Incidence >1%: None.

Incidence <1%: Hematuria; vaginal bleeding; proteinuria; nephrotic syndrome; interstitial nephritis; BUN elevation; renal insufficiency, including renal failure.

Hypersensitivity: Incidence >1%: None.

Incidence <1%: Acute anaphylaxis; acute respiratory distress; rapid fall in blood pressure resembling a shock-like state; angioedema; dyspnea; asthma; purpura; angiitis; pulmonary edema.

Metabolic: Incidence >1%: None.

Incidence <1%: Edema; weight gain; fluid retention; flushing or sweating; hyperglycemia; glycosuria; hyperkalemia.

Miscellaneous: Incidence >1%: None.

Incidence <1%: Epistaxis; breast changes, including enlargment and tenderness, or gynecomastia.

*Reactions occurring in 3 to 9% of patients treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked.)

The following local adverse reactions have been associated with the use of indomethacin suppositories: tenesmus, proctitis, rectal bleeding, burning, pain, discomfort and itching.

The following additional side effects have been reported; however a causal relationship to therapy with indomethacin has not been established.

Cardiovascular: thrombophlebitis.

Hematologic: Although there have been several reports of leukemia, the supporting information is weak.

Genitourinary: urinary frequency.

Table 1: Tabulation of Frequency of Adverse Reactions

Body System	**Frequency of Adverse Reactions**	
	Frequent (Incidence >1%)	**Rare (Incidence <1%)**
Gastrointestinal	Nausea* with or without vomiting; dyspepsia*(including indigestion, heartburn and epigastric pain), diarrhea, abdominal distress or pain, constipation.	Anorexia; bloating (including distention); flatulence; peptic ulcer; gastroenteritis; rectal bleeding; proctitis; single and multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small or large intestines; intestinal ulceration associated with stenosis and obstruction; gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.); development of ulcerative colitis and regional ileitis; ulcerative stomatitis; toxic hepatitis and jaundice (some fatal cases have been reported).
CNS	Headache; dizziness*; vertigo; somnolence; depression and fatigue (including malaise and listlessness).	Anxiety (includes nervousness); muscle weakness; involuntary muscle movements; insomnia; muzziness; psychic disturbances including psychotic episode; mental confusion; drowsiness; lightheadedness; syncope; paresthesia; aggravation of epilepsy and parkinsonism; depersonalization; coma; peripheral neuropathy; convulsions; dysarthria.
Dermatologic	None.	Pruritus; rash; urticaria; petechiae or ecchymosis; exfoliative dermatitis; erythema nodosum; loss of hair; Stevens-Johnson syndrome; erythema multiforme; toxic epidermal necrolysis.
Cardiovascular	None.	Hypertension; hypotension; tachycardia; chest pain; congestive heart failure; arrhythmia; palpitations.
Special Senses	Tinnitus.	Ocular-corneal deposits and retinal disturbances including those of the macula, have been reported in some patients on prolonged therapy with indomethacin; blurred vision; diplopia; hearing disturbances; deafness.
Hematologic	None.	Leukopenia; bone marrow depression; anemia secondary to obvious or occult gastrointestinal bleeding; aplastic anemia; hemolytic anemia; agranulocytosis; thrombocytopenic purpura; disseminated intravascular coagulation.

Body System	Frequency of Adverse Reactions	
	Frequent (Incidence >1%)	**Rare (Incidence <1%)**
Genitourinary	None.	Hematuria; vaginal bleeding; proteinuria; nephrotic syndrome; interstitial nephritis; BUN elevation; renal insufficiency, including renal failure.
Hypersensitivity	None.	Acute anaphylaxis; acute respiratory distress; rapid fall in blood pressure resembling a shock-like state; angioedema; dyspnea; asthma; purpura; angiitis; pulmonary edema.
Metabolic	None.	Edema; weight gain; fluid retention; flushing or sweating; hyperglycemia; glycosuria; hyperkalemia.
Miscellaneous	None.	Epistaxis; breast changes, including enlargement and tenderness or gynecomastia.

*Reactions occurring in 3 to 9% of patients treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Relatively little experience is available recording overdosage with indomethacin. Nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy may be observed. There have been reports of paresthesias, numbness, and convulsions. Signs of gastrointestinal hemorrhage could appear but have not been reported following the acute ingestion of large amounts of indomethacin accidentally or intentionally.

Treatment of overdosage:

Symptomatic and supportive treatment include emptying the stomach as quickly as possible by emesis or lavage if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 or 50 g of activated charcoal may be given. Depending on the condition of the patient, close medical observation and nursing care may be required.

The patient should be followed for several days because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. Use of antacids may be helpful.

DOSAGE AND ADMINISTRATION

Rhodacine is available in the following dosage form:
Rectal suppositories : 100 mg

Rhodacine suppositories are intended to supplement therapy using oral dosage forms of indomethacin.

In chronic disorders, treatment should be started with a dosage of 25 mg two or three times a day. By starting therapy with low dosage, increased gradually when necessary, maximum benefit will be produced with fewer adverse reactions.

Always give indomethacin with food, immediately after meals, or with antacids to reduce gastric irritation.

As with all drugs, the lowest possible effective dose should be utilized for each individual patient.

The drug should not be prescribed for children because safe conditions for use have not been established.

Since advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly.

Adult dosage recommendations:

Rheumatoid arthritis and ankylosing (rheumatoid) spondylitis:

Initial dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory

response is obtained or a dosage of 150 to 200 mg per day is reached. If a satisfactory response is not obtained with 200 mg a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 to 200 mg daily.

For patients with acute rheumatoid arthritis or with acute flares of chronic rheumatoid arthritis, increase the dosage daily by 25 mg until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg is reached. If adverse effects develop as the dosage is increased, the dosage should be reduced to a tolerated level for 2 or 3 days, and then, gradually increased by 25 mg every few days as tolerated. After the acute phase is under control, it is often possible to reduce the daily dosage gradually to 75 to 100 mg.

Reduction of steroid dosage:
Use of indomethacin often will permit a gradual reduction of steroid dosage by 25 to 50 percent. In some patients, steroids can be slowly discontinued over a period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

Severe osteoarthritis and degenerative joint disease of the hip:
Initial dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg a day is reached. If a satisfactory response is not obtained with 200 mg a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 to 200 mg daily.

Gout:

To control acute attacks: 50 mg three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

Use of Alternate Dosage Forms

Rhodacine suppositories:

The recommended dosage is 100 to 200 mg daily and should be individually adjusted to the patient's response and tolerance. Daily dose of 100 mg can be given as 50 mg twice daily or as 100 mg at night. Doses higher than 100 mg must be given on a twice daily schedule.

Combined administration:

One 50 mg or 100 mg suppository at bedtime, supplemented the following day by 25 mg capsules as needed up to a total of 150 mg to 200 mg of indomethacin. The total daily dose of indomathacin (capsules and suppositories) should not exceed 200 mg.

CHILDREN:

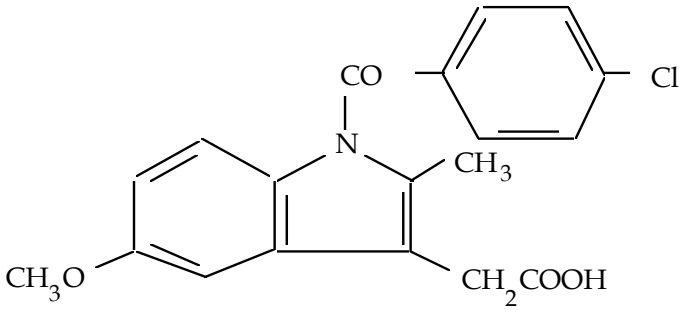
Rhodacine should not be prescribed for children because safe conditions for use have not been established (See Warnings).

PHARMACEUTICAL INFORMATION

Proper name: Indomethacin

Chemical name: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid

Structural formula:



Molecular weight: 357.81

Physical form: Pale yellow to yellow-tan, crystalline powder, having no more than a slight odor.

Solubility: Soluble in acetone, castor oil. Practically insoluble in water; sparingly soluble in alcohol, in chloroform and in ether.

pKa: 4.5

Melting point: 158-162°C

Composition: Each **Rhodacine** (indomethacin) suppository contains 100 mg indomethacin. Non-medicinal ingredients in alphabetical

order: Butylated hydroxyanisole, butylated hydroxytoluene, EDTA, glycerin, polyethylene glycol and sodium chloride.

Stability and storage recommendations: **Rhodacine** (indomethacin) 100 mg suppositories should be stored below 30°C. Protect from light and elevated humidity. Keep away from excessive heat. Preserve in well-closed containers, at controlled room temperature.

AVAILABILITY AND STORAGE

Rhodacine suppositories are available in 100 mg strengths. They are torpedo-shaped, smooth surfaced and yellowish-white in colour. They should be stored below 30°C. Protect from light and elevated humidity. Keep away from excessive heat. Preserve in well-closed containers, at controlled room temperature. Available in boxes of 30 suppositories.

INFORMATION TO THE PATIENT

Rhodacine (indomethacin), which has been prescribed to you by your physician, is one of a large group of nonsteroidal anti-inflammatory drugs (also called NSAIDs) and is used to treat the symptoms of certain types of arthritis such as rheumatoid arthritis, ankylosing spondylitis, gout and selected cases of osteoarthritis, including degenerative disease of the hip. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and by helping to control inflammation. NSAIDs do not cure arthritis, but they promote suppression of the inflammation and the tissue damaging effects resulting from this inflammation. This medicine will help you only as long as you continue to take it.

You should take **Rhodacine** (indomethacin) only as directed by your physician. 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 physician ordered. Taking too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly patient.

Be sure to take **Rhodacine** (indomethacin) 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 physician may decide to adjust the dosage according to your response to the medication.

STOMACH UPSET IS ONE OF THE COMMON PROBLEMS WITH NSAIDs:

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e. do not lie down) for about 15 to 30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your physician.

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

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

ALWAYS REMEMBER:

THE RISKS OF TAKING THIS MEDICATION MUST BE WEIGHED AGAINST THE BENEFITS IT WILL HAVE.

BEFORE TAKING THIS MEDICATION TELL YOUR PHYSICIAN AND PHARMACISTS IF YOU:

- or a family member are allergic to or have had a reaction to indomethacin or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), diclofenac, diflunisal, fenoprofen, fluriprofen, ibuprofen, ketoprofen, mefenamic acid, piroxicam, tiaprofenic acid, tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse);

- or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);

- have a history of stomach upset, ulcers, liver or kidney diseases;
- have blood or urine abnormalities;
- have high blood pressure;
- have diabetes;
- are on any special diet, such as a low-sodium or low-sugar diet;
- are pregnant or intend to become pregnant while taking this medication;

- are breast-feeding or intend to breast feed while taking this medication;
- are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporine, lithium, phenytoin and probenecid;

- have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.;
- have had an inflamed rectum or recent rectal bleeding (for **Rhodacine** suppositories).

WHILE TAKING THIS MEDICATION:

- tell any other physician, dentist or pharmacist that you consult or see, that you are taking this medication;

- some NSAIDs may cause drowsiness or fatigue in some people taking them. Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;

- check with your physician if you are not getting any relief of your arthritis or if any problems develop;

- report any untoward reactions to your physician. This is very important as it will aid in the early detection and prevention of potential complications;

- stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication;

- check with your physician immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;

- some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your physician;

- check with your physician immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;

- YOUR REGULAR MEDICAL CHECKUPS ARE ESSENTIAL.

SIDE EFFECTS OF THIS MEDICATION

Along with its beneficial effects, indomethacin like other NSAID drugs, may cause some undesirable reactions especially when used for a long time or in large doses.

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 PHYSICIAN 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, hives, swelling or itching;
- vomiting or persistent indigestion, nausea, stomach pain or diarrhea;
- yellow discoloration of the skin or eyes;
- any changes in the amount or colour of your urine (dark red or brown);
- any pain or difficulty experienced while urinating;
- swelling of the feet or lower legs;
- malaise, fatigue, loss of appetite;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness;
- hearing problems;
- constipation, headache, vertigo;
- ulcers or bleeding of the esophagus, stomach, duodenum or intestines may also occur;
- rectal bleeding or discomfort is sometimes associated with the use of **Rhodacine** suppositories.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your physician.

DOSING

In chronic disorders, treatment should be started with a dosage of 25 mg two or three times a day. By starting therapy with low dosage, increased gradually when necessary, maximum benefit will be produced with fewer adverse reactions.

Always give indomethacin with food, immediately after meals, or with antacids to reduce gastric irritation.

As with all drugs, the lowest possible effective dose should be utilized for each individual patient.

The drug should not be prescribed for children because safe conditions for use have not been established.

Since advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly.

Adult dosage recommendations:

Rheumatoid arthritis and ankylosing (rheumatoid) spondylitis:

Initial dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg per day is reached. If a satisfactory response is not obtained with 200 mg a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not

been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 to 200 mg daily.

For patients with acute rheumatoid arthritis or with acute flares of chronic rheumatoid arthritis, increase the dosage daily by 25 mg until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg is reached. If adverse effects develop as the dosage is increased, the dosage should be reduced to a tolerated level for 2 or 3 days, and then, gradually increased by 25 mg every few days as tolerated. After the acute phase is under control, it is often possible to reduce the daily dosage gradually to 75 to 100 mg.

Reduction of steroid dosage:

Use of indomethacin often will permit a gradual reduction of steroid dosage by 25 to 50%. In some patients, steroids can be slowly discontinued over a period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

Severe osteoarthritis and degenerative joint disease of the hip:

Initial dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg a day is reached. If a satisfactory response is not obtained with 200 mg a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 to 200 mg daily.

Gout:

To control acute attacks: 50 mg three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

Use of Alternate Dosage Forms:

Rhodacine suppositories**:**

The recommended dosage of **Rhodacine** suppositories is 100 to 200 mg daily and should be individually adjusted to the patient's response and tolerance. Daily dose of 100 mg can be given as 50 mg twice daily or as 100 mg at night. Doses higher than 100 mg must be given on a twice daily schedule.

Combined administration:

One 50 mg or 100 mg suppository at bedtime, supplemented the following day by 25 mg capsules as needed up to a total of 150 mg to 200 mg of indomethacin. The total daily dose of **Rhodacine** (capsules and suppositories) should not exceed 200 mg.

CHILDREN:

Rhodacine should not be prescribed for children because safe conditions for use have not been established (See Warnings).

WHAT YOU SHOULD DO IF YOU MISS A DOSE

If you miss a dose of **Rhodacine** and remember within an hour or so, take it right away. Then go back to your regular dosing schedule.

But if you do not remember until later, do not take the missed dose at all and do not double the next one. Instead, go back to your regular dosing schedule.

STORAGE

Rhodacine 100 mg suppositories should be stored below 30°C. Protect from light and elevated humidity. Keep away from excessive heat. Preserve in well-closed containers, at controlled room temperature.

Rhodacine IS NOT RECOMMENDED FOR USE IN CHILDREN SINCE SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED.

KEEP THIS PRODUCT AND ALL MEDICINE OUT OF THE REACH OF CHILDREN.

THIS MEDICATION HAS BEEN PRESCRIBED FOR YOUR MEDICAL PROBLEM. DO NOT GIVE IT TO ANYONE ELSE.

IF YOU REQUIRE MORE INFORMATION ON THIS DRUG, CONSULT YOUR PHYSICIAN OR PHARMACIST.

PHARMACOLOGY

Anti-inflammatory action:

The anti-inflammatory activity of indomethacin was first demonstrated in animals by measuring the ability of the compound to inhibit either granuloma formation or edema induced by subplantar injection of carageenan in rats. The rat paw edema assay appears to correlate well with anti-rheumatic activity in man.

Indomethacin was more potent than the other anti-rheumatic drugs as established by the ED_{50} determined in the anticarrageenan test method.

Substances	ED_{50}
Indomethacin	2.2
Mefenamic acid	9.0
Flufenamic acid	10
Phenylbutazone	25
Amidopyrine	31
Phenacetin	57
Aspirin	72
Phenazone	87
Acetaminophen	88
Cinchophen	92
Sodium salicylate	98

All these compounds produced anti-inflammatory activity at non-toxic doses. Good anti-inflammatory effect is exhibited in rats at 1/20th of the average human dose. Indomethacin was 2 times less active than piroxicam in the carrageenan-induced edema in rats.

When indomethacin was evaluated against aspirin, phenylbutazone, dexamethasone, mefenamic and flufenamic acid, for effects on the decrease in foot volume (which was used to evaluate the anti-inflammatory activity), indomethacin was found to be the most potent. Indomethacin was found to retain its effect even if the treatment was stopped.

The inhibition of carrageenan-induced edema by indomethacin is specific; the compound failed to inhibit edema induced by a variety of agents other than carrageenan, nor did it reduce edema if the drug was administered after the edema had been established.

As with other anti-inflammatory agents, the mechanism of action of indomethacin is unknown. But, in animals, indomethacin raises the level of ACTH and CS, and hence elevated the hypothalamo-hypopheseal adrenal axis secretory activity. This increased activity was associated with a reduced PG content. The mean site of action of systemically administered indomethacin on the hypothalamo-hypopheseal-adrenal axis was within the adeno hypophysis. This fact was verified in humans where indomethacin significantly increases the plasma growth hormone (HGH) level. Indomethacin is fully active in the absence of the adrenals and its activity is readily demonstrable by direct application of the compound to the site of action. Unlike anti-inflammatory steroids, indomethacin given to intact animals did not affect the size of the adrenals or the thymus, nor did it retard gain in body weight; these are sensitive indicators of adrenal activation. The anti-inflammatory activity of combinations of indomethacin and a steroid was greater than that of either drug alone in comparable doses.

Recent experiments have shown indomethacin to have a favorable effect upon adjuvant-induced polyarthritis in rats; it was more active than phenylbutazone or acetylsalicylic acid and less effective than prednisolone in suppressing the delayed manifestations of disseminated arthritis. This response is said to correlate well with clinical anti-arthritic activity.

Indomethacin has been found to be an effective anti-rheumatic agent in man. In fact, the rheumatic patients demonstrated a significant improvement of their rheumatic disease.

Antipyretic activity:

The antipyretic activity of indomethacin has been demonstrated in rabbits and rats injected with bacterial pyrogen, and in the classical yeast-induced fever assay in rats. Rectal administration of indomethacin produced a faster, stronger and longer antipyretic effect than oral ingestion.

No correlation between the effect of indomethacin on the content of prostaglandin and rectal temperature can be made: a dose-dependent effect is observed on the decreased content of prostaglandin without any effect on the rectal temperature.

A direct comparison of peak antipyretic activity in the yeast fever test showed indomethacin to be about 9 times as potent as aminopyrine, 24 times as potent as phenylbutazone, and 43 times as potent as acetylsalicylic acid.

The antipyretic activity of indomethacin has been confirmed clinically by observations in patients with a variety of febrile conditions. However, indomethacin should not be used as an antipyretic agent.

Analgesic activity:

Laboratory tests designed to detect mild analgesic activity indicate that indomethacin is more potent than acetylsalicylic acid or aminopyrine. In the phenylquinone writhing test, indomethacin was a better analgesic than piroxicam and much better than phenylbutazone: their respective ED_{50}'s are 0.25, 1.08 and 76 mg/kg in mice. Also, in this species, using another method to evaluate the analgesic activity, no analgesic activity was produced by indomethacin alone but, when combined with morphine, potentiated the morphine analgesia.

In man, indomethacin reduces the severity of pain and stiffness. Also, it is an effective analgesic in pleuritic chest pain. However, indomethacin should not be given as a simple analgesic.

ANIMAL TOXICOLOGY

Acute toxicity:

Species	LD_{50} (mg/kg) s.c.	p.o.	i.p.	i.v.
Mouse	--	50	28	40
Rat	13	12	15	--
Guinea-pig	--	543	40	--
Rabbit	--	130	--	--

Death often occurs an hour or so post-dosing. Signs were not apparent immediately. Before death, the animals showed decreased activity and ptosis. Most of the deaths resulted from gastrointestinal lesions.

Indomethacin possesses lower therapeutic indices than phenylbutazone and piroxicam as stated by their ratios of UD_{50} , PD_{50} and the LD_{50} to the ED_{50}.

	ED_{50}	Doses (mg/kg) UD_{50}	PD_{50}	LD_{50}
Indomethacin	7.4	2.0	4.5	14.2
Piroxicam	3.9	5.7	25.5	255
Phenylbutazone	91.0	230	390	665

At equieffective doses, piroxicam and indomethacin produced ulcers. However, the former drug had a lower tendency to produce ulcers than the latter one. For both drugs, the production of ulcers was dose-related. Indomethacin produced twice as many gastric ulcers as piroxicam in rats.

Indomethacin (2.5 to 20 mg/kg) produced ulceration in the glandular portion of the stomach. Indomethacin caused weight loss, melena, severe erosive gastritis and prepyloric or antral ulceration. The mechanism of ulceration during indomethacin

administration is a progressive necrosis with erosion of the glands in the antral mucosa. The ulcerogenicity of the compound was related to the mucosal prostacyclin (PGI_2) contents since these latter had a protective role on gastric mucosa.

Indomethacin was more ulcerogenic in the intestine than in the stomach. The direct contact mechanism was a much more important factor in the gastric ulcerogenicity of tolmetin sodium and ASA than in the ulcerogenicity of indomethacin. The presence of enterohepatic cycling might be a complicating factor for the ulcerogenic potential of indomethacin. When the bile duct was ligated, no intestinal lesions were produced while lesions were seen in normal control rats.

A single dose of 16 mg/kg of indomethacin, administered orally or subcutaneously, produced intestinal lesions in all treated rats, mostly in the middle segment of the small intestine. Starvation prevents the development of lesions. Bile duct ligation was as effective as starvation in preventing intestinal ulcers.

Chronic toxicity:

Indomethacin has been given to nine species in short and long term studies. However, with the exception of pigs and chickens, the human therapeutic dose is not well tolerated. The main toxic signs exhibited are inflammation and/or ulceration of the gastrointestinal mucosa and diarrhea.

Indomethacin toxicity was limited to ulcerative actions of the gastrointestinal tract. The doses as well as the site of toxic effect varied among species. However, the drug acted mostly in the ileum and jejunum. The toxic dose was higher than the anti-inflammatory one. The animals which survived a toxic dose recovered fully if the compound was withdrawn. Repeated administrations induced gastric lesions in dogs. An increase or significant increase of the lymphoid nodule of both the corpus and the antrum portions of the stomach was noted when indomethacin was administered once or repeatedly.

Reproduction studies:

Reproduction and teratogenic studies in mice, rats and rabbits showed no effect on fetal development or the reproduction cycle. There was some decrease in fetal viability and some delay in the onset of parturition in the rat, as has been observed with other nonsteroidal anti-inflammatory agents. A similar delay in the onset of parturition was not observed in the rabbit. Studies in mice demonstrated that indomethacin crosses the placental barrier.

During pregnancy, a significant increase of peptic ulcers in rats were observed.

Indomethacin did not exhibit any teratogenic or cytotoxic properties in cells of rat embryonic hindlimb buds. Indomethacin crossed the placenta at near parturition but not at the stage of organogenesis.

Carcinogenic and mutagenic studies:

Indomethacin regressed the proliferation of the cancer tumor in mice. Indomethacin significantly inhibited the DMBA-induced mammary carcinogenesis. The anti-carcinogenic mechanism of indomethacin is unknown. However, the chemoprevention produced by indomethacin was accompanied by treatment-related toxicity in certain groups.

Indomethacin exhibits mutagenic activity in mice.

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