PRODUCT MONOGRAPH

RHODIS®
(Ketoprofen)

100 mg Suppositories

RHODIS® EC

50 mg, 100 mg Enteric-Coated Tablets

Anti-Inflammatory Analgesic Agent

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NAME OF DRUG

RHODIS®
(Ketoprofen)

100 mg Suppositories

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THERAPEUTIC CLASSIFICATION

Anti-inflammatory analgesic agent.

ACTIONS AND CLINICAL PHARMACOLOGY

Animal pharmacological studies have shown that ketoprofen is a non-steroidal anti-inflammatory drug that possesses anti-inflammatory, analgesic and antipyretic properties. The anti-inflammatory action is not mediated through the pituitary adrenal axis.

Its therapeutic effectiveness has been demonstrated by a reduction in joint swelling, pain and duration of morning stiffness, and by increased grip strength and an improvement in functional capacity.

Clinical trials in rheumatoid arthritis have shown that the anti-arthritic activity of RHODIS (ketoprofen) 200 mg/day was similar to that of acetylsalicylic acid 3.6 g/day.

RHODIS® 200 mg daily induced less gastrointestinal bleeding than acetylsalicylic acid 4 g daily.

The effectiveness of RHODIS® as a general purpose analgesic has been studied in standard pain models which have shown the effectiveness of doses of 25 to 150 mg. Doses of 25 mg were superior to placebo. Larger doses than 25 mg generally could not be shown significantly more effective but there was a tendency toward faster onset and greater duration of action with 50 mg and, in the case of dysmenorrhea, a significantly greater effect overall with 75 mg. Doses greater than 50 to 75 mg did not have increased analgesic effect.

Pharmacokinetics properties:

In man, RHODIS® (ketoprofen) is rapidly and almost completely absorbed from the gastrointestinal tract. Maximum plasma levels are reached within 1/2 to 2 hours after administration of capsules or suppositories; however, peak plasma levels are delayed by a further 1 to 2 hours with enteric coated tablets and by 5 to 6 hours with sustained-release tablets. The biotransformation of ketoprofen is characterized by two main processes: hydroxylation and conjugation, the latter being the main metabolic pathway in man. The drug is 99% bound to plasma proteins, mainly to the albumin fraction. Metabolites as well as the unchanged drug are excreted mainly in the urine. Fecal excretion is negligible.

Following the administration of capsules or enteric coated tablets in man, 25% to 90% of the drug is excreted in the urine within 24 hours, with the major portion being excreted during the first 6 hours. The elimination half-life is approximately 2 hours. Following administration of slow release ketoprofen, absorption is gradual reaching a plateau during which plasma levels remain steady from the fifth to the twelfth hour after ingestion and decrease with an apparent half-life of 3 to 4 hours. No accumulation of ketoprofen was found following repeated once-daily administration of ketoprofen sustained-release tablets. Repeated administration of the drug, in both animals and man, caused no induction of liver enzymes.

When ketoprofen capsules are administered with food, the total bioavailability (AUC) is not altered; however, the rate of absorption is slowed resulting in delayed and reduced peak concentrations (Cmax). Following a single 50 mg dose of RHODIS® while fasting, the mean Cmax was 4.1 mg/L (at 1.1 hours); when administered after food, it decreased to 2.4 mg/L (at 2.0 hours).

The composition of the diet slightly but significantly alters the extent of absorption of ketoprofen from sustained-release tablets: a high-fat/high-calory meal (3000 calories/day) was associated with lower ketoprofen bioavailability values (about 20%) than a low-fat/low-calory content ($\leq$1200 calories/day). Mean trough ketoprofen plasma concentrations were similar after high or low fat meals.

To date, studies of the effects of age and renal-function impairment have been small, generally involving 5 to 8 subjects per group, but they indicate modest decrease in clearance in the elderly and in patients with impaired renal function. In normal elderly volunteers (mean age 73 years), the plasma and renal clearance and protein-binding were reduced while the V_d increased when compared to a younger normal population (mean age 27 years). (Plasma clearance and V_d were 0.05 L/kg/hr and 0.4 L/kg in elderly and 0.06 L/kg/hr and 0.3 L/kg in young subjects, respectively). The mean half-life of RHODIS® in this normal geriatric population, as well as in a rheumatoid elderly population (mean age 64 years), was about 5 hours as compared to 3 hours in the younger population.

Patients with impaired renal function (mean age 44 years) also demonstrate decreases in plasma clearance (0.04 L/kg/hr) of drug, with the mean half-life increasing to about 3.5 hours.

INDICATIONS AND CLINICAL USES

RHODIS® (ketoprofen) is indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis.

RHODIS® is also indicated for the treatment of primary dysmenorrhea as well as for the relief of mild to moderate acute pain associated with musculotendinous trauma (sprains and strains), postoperative (including dental surgery) or postpartum pain.

CONTRAINDICATIONS

RHODIS® (ketoprofen) is contraindicated in patients with active peptic ulcers, a history of recurrent ulceration or active inflammatory diseases of the gastrointestinal tract; suppositories should not be used in patients with any inflammatory lesions of rectum or anus and in patients with a recent history of rectal or anal bleeding.

RHODIS® is contraindicated in patients with known or suspected hypersensitivity to the drug or other non-steroidal anti-inflammatory drugs (NSAIDs). Because of cross-sensitivity, ketoprofen should not be given to patients with the complete or partial syndrome of nasal polyps, or asthma, anaphylaxis, rhinitis or urticaria. Fatal anaphylactoid reactions have occurred in such individuals.

Significant hepatic impairment or active liver disease.

Severely impaired or deteriorating renal function (creatinine clearance < 30 mL/min or 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.

RHODIS® 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.

WARNINGS

Gastrointestinal (GI) system:
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 (NSAID's) including RHODIS® (ketoprofen). Unlike most adverse reactions, which usually manifest themselves in the first month if they are going to occur in an individual, new peptic ulcers keep appearing in patients under treatment with ketoprofen at a rate of greater than 1% per year.

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 non-steroidal 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.

RHODIS® 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, ketoprofen should be discontinued immediately, appropriate treatment instituted and the patients 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 frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs. The incidence of the 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)

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

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: The safety of RHODIS® when administered to pregnant or nursing women has not been determined and therefore such use is not recommended. Pregnant rats who received ketoprofen 6 and 9 mg/kg/day p.o. from day 15 of gestation, showed dystocia and increased pup mortality.

Nursing mothers: In rats, RHODIS® at doses of 9 mg/kg (approximately 1.5 times the maximum human therapeutic dose) did not affect perinatal development. Upon administration to lactating dogs, the milk concentration of RHODIS® was found to be 4 to 5% of the plasma drug level. Data on secretion in human milk after ingestion of ketoprofen do not exist. As with other drugs that are excreted in milk, RHODIS® is not recommended for use in nursing mothers.

Use in Children: The conditions for safe and effective use of RHODIS® in children under 12 years of age have not been established and the drug is therefore not recommended in this age group.

PRECAUTIONS

Gastro-intestinal 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 RHODIS® (ketoprofen) therapy when and if these adverse reactions appear.

Suppositories should be given with caution to patients with any rectal or anal pathology.

Renal function:
Long-term administration of nonsteroidal anti-inflammatory drug (NSAID) to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greastest 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 pre-treatment state.

RHODIS® 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 RHODIS® should be considered and patients carefully monitored.

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

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 ketoprofen 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, 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. Meaningful (3 times the upper limit of normal) elevations of ALT or AST occurred in controlled clinical trials in less than 1% of patients. 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 approximately 2% of patients treated with RHODIS®. 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. RHODIS® 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 RHODIS® is administered.

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

Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by nonsteroidal anti-inflammatory drugs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients with initial hemoglobin values of 10 g/dL or less who are to receive long-term therapy should have hemoglobin values determined frequently.

Infection:
In common with other anti-inflammatory drugs, RHODIS® may mask the usual signs of infection.

Ophthalmology:
Blurred and/or diminished vision has been reported with the use of RHODIS® and other non-steroidal 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 ketoprofen. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Drug Interactions: Methotrexate: The concomitant administration of ketoprofen and high-dose methotrexate has been associated with prolonged and marked enhancement of serum methotrexate levels resulting in severe methotrexate toxicity. This may also apply to some other non-steroidal anti-inflammatory drugs. There were no abnormalities in methotrexate kinetics or evidence of toxicity when ketoprofen was given at least 12 hours after completion of high-dose methotrexate infusion. RHODIS® should not be used in patients receiving high dose methotrexate.

The potential for severe toxicity should be kept in mind when prescribing ketoprofen and low-dose methotrexate concurrently. RHODIS® should not be administered within 12 hours of methotrexate infusion.

Acetylsalicylic acid (ASA) or other NSAIDs: Concurrent administration of ASA decreased ketoprofen protein binding and increased its plasma clearance. The overall result was a 40% reduction in the AUC of ketoprofen. RHODIS® does not alter ASA absorption.

The use of RHODIS® 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. Concurrent therapy may increase the risk of gastrointestinal toxicity, including ulceration of hemorrhage, without providing additional symptomatic relief. Concurrent use of ASA with other NSAIDs may also increase the risk of bleeding at sites other than the gastrointestinal tract because of additive inhibition of platelet aggregation.

Oral anticoagulants: RHODIS® has been shown to depress platelet aggregation and it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. However, a study conducted in twenty patients undergoing therapy with coumarin and simultaneously receiving RHODIS®, failed to demonstrate potentiation of anticoagulant effect. Nevertheless, close monitoring of patients is recommended when RHODIS® is given concomitantly with 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.

Diuretics: Hydrochlorothiazide, given concomitantly with RHODIS®, produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition. Concurrent use of a potassium-sparing diuretic with some NSAIDs may increase the risk of hyperkalemia.

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

Antacids: concomitant administration of magnesium hydroxide and aluminium hydroxide does not interfere with the rate or extent of the absorption of ketoprofen.

Lithium: nonsteroidal anti-inflammatory agents have been reported to increase steady-state plasma lithium levels. It is recommended that plasma lithium levels be monitored when RHODIS® is coadministered with lithium.

Probenecid: concurrent administration of probenecid increases both free and bound ketoprofen through reducing the plasma clearance of ketoprofen to about one-third as well as decreasing its protein binding. RHODIS® is not recommended in association with probenecid.

RHODIS® 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.

Clinical Laboratory Test: The presence of RHODIS® and its metabolites in urine has been shown to interfere with certain tests which are used to detect albumin, bile salts, 17-ketosteroids or 17-hydroxycorticosteroids in urine and which rely upon acid precipitation as an end point or upon color reactions for carbonyl groups. No interference was seen in the tests for proteinuria using Albustix, Hema-Combistix or Labstix Reagent Strips.

RHODIS® 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 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.

Cyclosporine:
Inhibition of renal prostaglandin by NSAIDs may increase the plasma concentration of cyclosporine and the risk of cyclosporine-induced nephrotoxicity. Patients should be carefully monitored during concurrent use.

Digoxin:
The possibility should be considered that some NSAIDs may increase digoxin concentrations, leading to an increased risk of digitalis toxicity. Increased monitoring and dosage adjustments of digoxin may be necessary during and following concurrent NSAID therapy. However, ketoprofen may have no effect on digoxin concentrations.

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.

ADVERSE REACTIONS

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

In clinical trials of RHODIS® (ketoprofen) involving 1542 patients, the most common side effects reported were gastrointestinal (22%). The most severe were peptic ulcer or GI bleeding which occurred in controlled clinical trials in less than 1% of 1076 patients; however, in open label continuation studies in 1292 patients, the rate was greater than 2%.

The detailed breakdown of side effects with their corresponding frequencies (not indicated when <1%) is given herewith. That includes rare adverse reactions collected from foreign reports to manufacturers and regulatory agencies, publications and U.S. clinical trials:

Gastrointestinal (22%): dyspepsia (12.8%), nausea (4.0%), indigestion and flatulence (2.8%), vomiting (2.0%), constipation (2.0%), diarrhea (1.4%), anorexia, ulcer, GI bleeding and perforation, melena, hematemesis, stomatitis.

Rectal administration was associated with a lower incidence of upper gastrointestinal reactions (12%) with the exception of ulceration, the incidence of which was the same. However, ano-rectal reactions presenting as local pain, burning, pruritus, tenesmus and rare instances of rectal bleeding occurred in 16.5% of subjects. Five per cent of patients discontinued rectal therapy because of these local reactions.

Central Nervous System (3-5%): headache (1.7%), fatigue (1%), dizziness, tension, anxiety, depression, drowsiness, impotence, vertigo, migraine, paresthesia.

Body as a whole: angioedema, asthma, life threatening bronchospasm, anaphylaxis.

Dermatologic (<3%): rashes (1.7%), pruritus, flushing, excessive perspiration, alopecia, bullous rash, exfolliative dermatitis, photosensitivity, purpuric rash, urticaria, onycholysis.

Cardiovascular: peripheral edema (2%), palpitation, congestive heart failure, hypertension.

Special senses: tinnitus, hearing impairment, visual disturbance, conjunctivitis, conjunctivitis sicca, taste perversion.

Hematologic: hypocoagulability, agranulocytosis, anemia, hemolysis, purpura, thrombocytopenia.

Renal: interstitial nephritis, hematuria, nephrotic syndrome, impairment of renal function, acute renal failure.

Hepatic: hepatic dysfunction, jaundice.

Laboratory tests: Abnormal alkaline phosphatase lactic dehydrogenase, glutamic oxaloacetic transaminase and blood urea nitrogen values were found in some patients receiving RHODIS® therapy. The abnormalities did not lead to discontinuation of treatment and, in some cases, returned to normal while the drug was continued. There have been sporadic reports of decreased hematocrit and hemoglobin values without progressive deterioration on prolonged administration of the drug.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: Of 20 cases of overdosage (up to 5,000 mg) reported in Great Britain (5 children, 14 adolescents or young adults, and 1 elderly), only 4 had mild symptoms (vomiting in 3, drowsiness in 1 child).

Treatment: Administer gastric lavage or an emetic and treat symptomatically: compensate for dehydration, monitor urinary excretion and correct acidosis if present.

The drug is dialyzable; therefore, hemodialysis may be useful to remove circulating drug and to assist in case of renal failure.

DOSAGE AND ADMINISTRATION

ADULTS

Rheumatoid arthritis and osteoarthritis:

Oral: The usual dosage for RHODIS® (ketoprofen) enteric coated tablets is 150 to 200 mg per day in 3 or 4 divided doses.

Once the maintenance dosage has been established, patients may be tried on a twice daily dosing regimen. Clinical trials, however, show that some rheumatoid arthritis patients respond better to more frequent dosing. The usual maintenance dose is 100 mg twice daily.

Rectal: RHODIS® suppositories offer an alternative route of administration for those patients who prefer it. Administer one suppository morning and evening or one suppository at bedtime supplemented as needed by divided oral doses.

The total daily dose of RHODIS® tablets and suppositories should not exceed 200 mg per day. When the patient's response warrants it, the dose may be decreased to the minimum effective level.

In severe cases, during a flare-up of rheumatic activity or if a satisfactory response cannot be obtained with the lower dose, a daily dosage in excess of 200mg may be used. However, a dose of 300 mg per day should not be exceeded.

Primary dysmenorrhea and mild to moderate pain:

Oral: The usual dose for RHODIS® (ketoprofen) is 50 mg 3 or 4 times daily as necessary.

A larger dose may be tried if the patient's response to a previous dose was less than satisfactory, but individual doses above 50 mg have not been shown to give added analgesia. The total daily dose should not exceed 300 mg. In most types of acute pain, a course of 3 to 7 days has been shown to be sufficient.

ELDERLY and DEBILITATED PATIENTS

Initial dosage should be reduced by 1/2 to 1/3 in patients with impaired renal function and the elderly.

CHILDREN

RHODIS® is not indicated in children under 12 years of age because clinical experience in this group of patients is insufficient.

AVAILABILITY

RHODIS® (ketoprofen) is available as:

Suppositories:	100mg cream white, torpedo-shaped suppository, marked “RHODIS” over “100mg” in green. 3 blister strips of 10 suppositories each.
Enteric-coated tablets:	50 mg and 100 mg yellow, round, biconvex, enteric-coated tablets, plain on one side and identified 50 or 100 on the other. Bottles of 100 and 500.

INFORMATION TO THE PATIENT

NAME AND INDICATIONS

RHODIS® which has been prescribed to you by your doctor, is one of a large group of non-steroidal anti-inflammatory drugs (NSAID's) and is used to treat the symptoms of certain types of arthritis. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and 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.

RHODIS® may also be used for treating mild to moderate acute pain, including menstrual cramps.

HOW TO USE THIS MEDICINE

You should take RHODIS® only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered. 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 RHODIS® regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

If you are taking RHODIS® enteric-coated tablets (RHODIS® EC) take them preferably one to two hours before meals or at least two hours after meals. Swallow your tablets whole. Do not break, crush or chew.

IF YOU MISS A DOSE...

If you miss a dose of RHODIS® enteric-coated tablets, take it as soon as possible. However if it is almost time for your next dose, skip the missed dose and go back to your regular schedule.

NEVER DOUBLE DOSES

RHODIS® IS NOT RECOMMENDED FOR USE IN PATIENTS UNDER 12 YEARS OF AGE SINCE SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED.

KEEP OUT OF THE REACH OF CHILDREN.

IMPORTANT NOTICE

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

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

SIDE EFFECTS

Along with its beneficial effects, RHODIS® 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 doctor immediately if any of the following are noted:

- bloody or black tarry stools;
- shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
- skin rash, swelling, hives or itching;
- persistent indigestion, nausea, vomiting, stomach pain or diarrhea;
- yellow discoloration of the skin or eyes, with or without fatigue;
- any changes in the amount or colour of your urine (such as dark; red or brown);
- any pain or difficulty experienced while urinating;
- swelling of the feet or lower legs;
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness, hearing problems.

ALWAYS REMEMBER

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

- or a family member are allergic to or have had a reaction to RHODIS® or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, mefenamic acid, nabumetone, piroxicam, tenoxicam, sulindac, tiaprofenic acid or tolmetin 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, or 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;
- are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, cyclosporine, methotrexate, lithium, phenytoin;
- have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

While taking this medication:

- tell any other doctor, 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 doctor if you are not getting any relief or if any problems develop.
- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- 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 doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark and 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 doctor;
- check with your doctor 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.

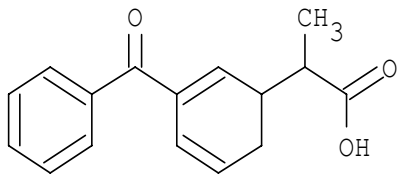
Your regular medical checkups are essential.

If you require more information on this drug, consult your doctor or pharmacist.

This medication has been prescribed for your medical condition. Do not give it to anyone else. Keep this and all medication out of the reach of children.

CHEMISTRY

Ketoprofen is m-benzoylhydratropic acid. Its structural formula is as follows:



Molecular formula: $C_{16}H_{14}O_3$ Molecular Weight.: 254.3

Description

Ketoprofen is a white crystalline, odourless, non-hygroscopic powder. Its melting point is approximately 93°C. It is very soluble in ether, ethanol, chloroform and acetone; soluble in benzene and very slightly soluble in water.

PHARMACOLOGY

Anti-inflammatory activity

In a battery of tests, ketoprofen on a mg/kg basis, exhibited a potent anti-inflammatory activity (see table).

Test	ED_{50} (mg/kg)	Route of administration
Carrageenin induced abcess (Rat)	0.85 - 2.0 0.22	p.o. s.c.
Carrageenin induced oedema (Rat)	7.5 - 9	p.o.
U.V. induced erythema (Guinea pig)	6	p.o.
Selye's granulomatous pouch (Rat)	12	p.o.
Granuloma induced by asbestos implant (Rat)	15	p.o.

Analgesic activity: In the mouse, oral ketoprofen showed an analgesic effect on the visceral pain induced by phenylbenzoquinone. In this test, the ED_{50} was of 5mg/kg p.o. In the rat, against pain induced by pressure applied on an inflamed paw, the ED_{50} of ketoprofen was 1.6 mg/kg p.o.

Antipyretic activity: In the hyperthermia induced by brewer's yeast in rats, oral ketoprofen had an ED_{50} of 0.5 mg/kg. Against the hyperthermia induced by the injection of an antigonococcal vaccine in rabbits, ketoprofen exhibited an antipyretic effect at dosages of 1 and 2 mg/kg s.c. The drug had no hypothermic effects in normal rats and rabbits.

Antibradykinin activity: Ketoprofen was tested for antibradykinin activity against the bronchospasm induced by intravenous bradykinin in the guinea pig and on the visceral pain caused by the intraperitoneal injection of bradykinin in the mouse. The ED_{50}s of the drug were respectively 0.025 mg/kg I.V. and 6.2 mg/kg p.o. in these experiments.

Inhibition of prostaglandin synthesis: In the isolated guinea pig lung, ketoprofen exerted a marked inhibitory effect on the biosynthesis of prostaglandins induced by arachidonic acid. In passively immunized human isolated lung tissues, ketoprofen at concentrations of 0.1, 0.2 and 0.3 mg/mL significantly inhibited the biosynthesis of prostaglandins E_2 and F_2 induced by antigenic challenge, both prostaglandins being affected to the same extent.

Inhibition of platelet aggregation:
In the rabbit, ketoprofen 0.5 mg/kg p.o. inhibited platelet aggregation induced in vitro by collagen in platelet-rich plasma of treated animals. In vivo in the rabbit, ketoprofen at 0.1 mg/kg p.o. had an inhibitory effect on arachidonic acid induced aggregation of platelets in the pulmonary vessels.

Interaction between ketoprofen and warfarin in rats and dogs:
In rats, ketoprofen administered orally at a daily dose of 3 or 6 mg/kg concomitantly with warfarin, did not alter the acute toxicity of the latter drug.

In dogs, oral administration of ketoprofen 3 mg/kg/day for 3 weeks caused no modification of the hypoprothrombinemia induced by daily oral administration of warfarin.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

Ketoprofen is almost completely absorbed whether administered orally as capsules, enteric-coated or sustained-release tablets or rectally as suppositories. Absorption is rapid after administration of the drug as an oral capsule or rectally with peak plasma concentrations occurring between 0.5 to 2 hours. Peak plasma levels are delayed by a further 1 to 2 hours with the enteric-coated tablets and by 5 to 6 hours with the sustained-released tablets. Food slows the rate of absorption of ketoprofen with the capsule formulation, resulting in delayed and reduced peak plasma concentrations, but the extent of absorption is not affected. Following single 50 mg capsules doses, the mean Cmax of 4.1 mg/L occur after about 1 hour in the fasted state compared with 2.4 mg/L after 2 hours in the non fasted state. Concomitant administration of an aluminium and magnesium hydroxides antacid or an aluminium phosphate antacid does not appear to affect absorption of the drug.

The composition of the diet slightly but significantly alters the extent of absorption of ketoprofen from sustained-release tablets: a high-fat/high-calory meal (≈ 3000 calories/day) was associated with lower ketoprofen bioavailability values (about 20%) than a low-fat/low-calory content (≈ 1200 calories/day). Mean trough ketoprofen plasma concentrations were similar after high or low fat meals.

The area under the plasma concentration time curve (AUC) are linearly related to dose over the range of 75 - 200 mg and neither accumulation nor induction of liver enzymes occur after repeated doses. There is considerable inter-individual and intra-individual variation in plasma concentrations attained with a given dosage. Although the relationship between plasma ketoprofen concentrations and therapeutic effect has not been precisely determined, a therapeutic range of 0.4 - 6 mg/L has been suggested.

Distribution

Like other NSAIDs, ketoprofen is highly (≈ 99%) protein bound. The apparent volume of distribution (Vd) is approximately 0.1 L/kg. The drug efficiently penetrates inflamed synovial fluid where peak concentrations are about 30% of those in plasma; by 4 - 6 hours after administration, synovial fluid concentrations exceed those in plasma.

Metabolism

Ketoprofen is rapidly and extensively metabolized in the liver, principally by hydroxylation and conjugation; the latter being the main metabolic pathway in man. Metabolites as well as the unchanged drug are excreted mainly in the urine; fecal excretion is negligeable. Following the administration of capsules or enteric coated tablet, 25% to 90% of the drug is excreted in the urine within 24 hours, with the major portion being excreted during the first 6 hours.

Elimination

In healthy volunteers, the apparent plasma clearance of ketoprofen averages approximately 1 - 1.3 mL/min/kg and the elimination half-life is approximately 2 hours.

Total apparent plasma clearance of the drug is decreased in patiehts with reduced renal function. In a group of patients with creatinine clearance of 20 - 60 mLmin, total apparent plasma clearance averaged 0.7 mL/min/kg. Total apparent plasma clearance is also similarly decreased in geriatric

individuals, resulting in an increase in elimination half-life (2.7 hours *vs* 1.77 hours in younger population).

TOXICOLOGY

Acute Toxicity

Ketoprofen LD_{50}s are as follows:

SPECIES	ORAL	I.V.	S.C.
Mouse	360 mg/kg	500 mg/kg	550 mg/kg
Rat	160 mg/kg	--	100 mg/kg
Guinea pig	1300 mg/kg	450 mg/kg	--

A comparison of the LD_{50}s found in weanling and adult rats after single, or repeated oral dosing on five consecutive days, revealed that the toxicity of ketoprofen was some 13 to 15 times lower in weanling rats than in adult animals. A study of the comparative pharmacokinetics of ketoprofen in these two age groups suggests that this difference in toxicity may be due to a difference in the rate of absorption, metabolism and excretion found between both groups: a lower peak plasma concentration was measured in weanling rats as compared to that in the adults, the drug was considerably less metabolized and urinary excretion was much faster in young rats than in adult animals.

Subacute and chronic toxicity

Rat

Ketoprofen was administered orally to rats at doses ranging from 2 to 36 mg/kg/day for 1 month, 6 to 24 mg/kg/day for 3 months and 4.5 to 12.5 mg/kg/day for 18 months.

The main pathological findings were gastrointestinal irritation and ulceration, the severity of which was related to the dose administered and to the length of exposure. These changes occurred with doses of 7.5 mg/kg/day and above.

At doses of 18 mg/kg/day p.o. for one month and 12 mg/kg/day p.o. for 3 months, changes in the gastric mucosa were less severe while doses of 27 and 36 mg/kg/day for one month, 24 mg/kg/day for 3 months and 7.5 and 12.5 mg/kg/day for 18 months produced serious gastric ulceration leading to an increased mortality incidence. On chronic oral administration, nephropathy was observed at all doses. The changes involved both cortex and papilla and were extensive at higher doses.

Dog

In the dog, daily oral doses of 2, 6, 18 and 36 mg/kg for 1 month and 3, 6, 12 and 24 mg/kg for 3 months were administered. At doses of 3, 6 and 12 mg/kg for 3 months, gastric ulcerations were revealed at autopsy. At daily doses of 18 and 36 mg/kg for 1 month and of 24 mg/kg for 3 months, there was weight loss, severe dose-related gastric ulceration, anemia with occasional hyperleukocytosis, and, in a few males, testicular involution; laboratory determinations revealed, in some animals, decreases in serum total protein content and albumin/globulin ratio, hyper-fibrinemia and an increase of the erythrocyte sedimentation rate.

Baboon

Ketoprofen was administered at oral doses of 4.5, 9 and 27 mg/kg/day for one year. Two control groups received either lactose or indomethacin 4.5 mg/kg/day.

No abnormal clinical signs were recorded with either ketoprofen or indomethacin. There was temporary suppression of weight gain during the first six weeks in animals receiving 27 mg/kg of ketoprofen.

Post-mortem examination revealed a variety of minor changes in the gastrointestinal tract which in the main consisted of areas of congestion, small depressions and minimal erosions. These were present in all test groups, including the control groups.

Two out of twelve animals receiving 27 mg/kg, the first sacrificed after 26 weeks, and the second after one year, showed an area of scarring in the pyloric antrum which suggested a healed ulcer.

CARCINOGENICITY and MUTAGENICITY

The carcinogenic potential of ketoprofen was studied in C_{57}Bl/6/Rho-Ico mice. The drug was administered in drinking water at dosages of 2, 4, 8, 16 and 32 mg/kg/day for 105 weeks.

Tumours observed in control and treated groups showed no pattern indicative of carcinogenicity. There was a dose-related incidence of endometrial hyperplasia.

Ketoprofen did not show mutagenic potential in the Ames test.

REPRODUCTION STUDIES

In the rat, ketoprofen was administered orally at dosages of 3, 6 and 9 mg/kg daily. In males, the drug was administered during 11 consecutive weeks, mating with untreated females taking place during the last week of dosing. In females, ketoprofen was administered during the two weeks which preceded mating with untreated males, the mating period and the two first weeks of gestation.

At 9 mg/kg, 4 out of 17 males and 2 out of 36 females died with definite signs of gastrointestinal damage. However, with the exception of a slightly decreased implantation rate observed in females receiving the two higher dosages (not dose related), ketoprofen exerted no effects on fertility and on the general reproductive functions of male and female rats.

Teratogenicity studies with ketoprofen were conducted in mice, rats and rabbits, using the following dosage schedules:

Mice: 3, 6 and 12 mg/kg p.o. from day 5 to 15 of pregnancy.
Rats: 3, 6 and 9 mg/kg p.o. from day 5 to 15 of pregnancy.
Rabbits: 2, 3, 4, 6 and 12 mg/kg p.o. from day 6 to 16 of pregnancy.

In these studies, there was no evidence of drug induced teratogenic activity.

Female rats were given oral ketoprofen 3, 6 and 9 mg/kg from day 15 of gestation through lactation, to 21 days post partum. Rats receiving indomethacin 1.5, 3 and 6 mg/kg were used as controls.

Both drugs exerted an inhibitory effect on the ultimate stage of pregnancy and on parturition; a large number of animals treated at the intermediate and high dosage levels died either just before, during or shortly after parturition with evidence of dystocia. The maximum tolerated dosage was about 3 mg/kg per day. At this level, litter parameters from birth through lactation to weaning appeared unaffected by treatment. No malformations were observed among the young born to treated mothers.

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