PRODUCT MONOGRAPH

KETOPROFEN

Ketoprofen Capsules BP

50 mg

KETOPROFEN-E

Ketoprofen Enteric-coated Tablets

50 mg and 100 mg

KETOPROFEN SR

Ketoprofen Sustained-release Tablets

200 mg

Anti-inflammatory, analgesic agent

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THERAPEUTIC CLASSIFICATION

Anti-inflammatory, analgesic agent

ACTIONS AND CLINICAL PHARMACOLOGY

Animal pharmacological studies have shown that ketoprofen is a NSAID 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 ketoprofen 200 mg/day was similar to that of acetylsalicylic acid 3.6 g/day.

Ketoprofen 200 mg daily induced less gastrointestinal bleeding than acetylsalicylic acid 3.6 g daily.

The effectiveness of ketoprofen 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

In man, 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; 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 (C_{max}). Following a single 50 mg dose of ketoprofen while fasting, the mean C_{max} 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 calorie meal (3000 calories/day) was associated with lower ketoprofen bioavailability values (about 20%) than a low-fat/ low-calorie content (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 ketoprofen 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.

Comparative Bioavailability

Bioavailability studies were performed using normal human volunteers. The rate and extent of absorption of ketoprofen after a single oral 50 mg dose of ORUDIS® 50 mg and KETOPROFEN 50 mg capsules were measured and compared. The results are summarized as follows:

	ORUDIS® 50 mg	KETOPROFEN 50 mg	% Diffr.
AUC_{0-12} (μg. hr/mL)	9.93	9.49	-4.4
C_{max} (μg/mL)	5.31	4.39	-17.3
T_{max} (hr)	1.12	1.35	+20.4
$t_{1/2}$ (hr)	1.7	1.6	-5.9

The rate and extent of absorption of ketoprofen after a single oral 50 mg dose of ORUDIS® E 50 mg and KETOPROFEN-E 50 mg enteric-coated tablets were measured and compared. The results are summarized as follows:

	ORUDIS® E 50 mg	KETOPROFEN-E 50 mg	% Diffr.
AUC_{0-12} (μg. hr/mL)	9.59	9.72	+1.4
C_{max} (μg/mL)	6.09	4.41	-27.7
T_{max} (hr)	1.5	1.6	+10.6
$t_{1/2}$ (hr)	1.8	1.8	0.0

Two additional bioavailability studies were performed using sustained-release tablets, one with food and one without food. The rate and extent of absorption of ketoprofen after a single oral 200 mg dose of ORUDIS® SR 200 mg and KETOPROFEN SR 200 mg tablets were measured and compared. The results from measured data are summarized as follows:

Study 1 (Without Food)

	Geometric Mean Arithmetic Mean (CV%)		
Parameter	Ketoprofen SR	Orudis® SR†	Ratio of Means (%)
AUC_T (μg.hr/mL)	30.3 31.0 (19)	31.2 31.7 (19)	96.9*
AUC_I (μg.hr/mL)	34.5 35.1 (19)	35.5 36.1 (21)	97.1*
AUC_x (μg.hr/mL)	30.3 31.9 (19)	31.2 31.6 (19)	97.2*
C_{max} (μg/mL)	3.32 3.45 (32)	3.29 3.39 (28)	99.7*
T_{max} (hr)	10.2 (37)	7.08 (45)	-
$t_{1/2}$ (hr)	2.93 (23)	3.87 (53)	-

The T_{max} and $t_{1/2}$ parameters are expressed as the arithmetic means.

† Orudis® SR (Rhône-Poulenc Rorer) was purchased at a Canadian retail pharmacy.

*Based on the least squares estimate of the geometric means.

Study 2 (With Food)

Parameter	Geometric Mean Arithmetic Mean (CV%) Ketoprofen SR	Orudis® SR†	Ratio of Means (%)
AUC_T (μg.hr/mL)	26.6 29.5 (44)	26.0 28.7 (45)	98.4*
AUC_I (μg.hr/mL)	30.6 33.5 (39)	29.4 32.2 (42)	97.6*
AUC_x (μg.hr/mL)	25.3 27.9 (43)	24.3 26.3 (39)	101.8*
C_{max} (μg/mL)	3.46 3.53 (20)	3.94 4.14 (29)	82.2*
T_{max} (hr)	11.9 (39)	9.69 (61)	-
$t_{1/2}$ (hr)	3.13 (53)	2.15 (41)	-

The T_{max} and $t_{1/2}$ parameters are expressed as the arithmetic means.

† Orudis® SR (Rhône-Poulenc Rorer) was purchased at a Canadian retail pharmacy.

*Based on the least squares estimate of the geometric means.

INDICATIONS AND CLINICAL USE

KETOPROFEN is indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis.

KETOPROFEN 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

KETOPROFEN is contraindicated in patients with active peptic ulcers or active inflammatory diseases of the gastrointestinal tract.

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

WARNINGS

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

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

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or

gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

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

Use in Pregnancy

The safety of KETOPROFEN 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, ketoprofen 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 ketoprofen 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, KETOPROFEN is not recommended for use in nursing mothers.

Use in Children

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

PRECAUTIONS

Gastrointestinal System

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs, KETOPROFEN should be discontinued, an appropriate treatment instituted and the patient closely monitored.

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

Renal Function

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

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the

pre-treatment state.

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

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

Hepatic Function

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur 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 this drug as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

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

Fluid and Electrolyte Balance

Fluid retention and edema have been observed in approximately 2% of patients treated with ketoprofen. 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. KETOPROFEN should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

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

Hematology

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

Blood dyscrasias associated with the use of nonsteroidal 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, KETOPROFEN may mask the usual signs of infection.

Ophthalmology

Blurred and/or diminished vision has been reported with the use of ketoprofen and other NSAIDs. If such symptoms develop KETOPROFEN should be discontinued and an ophthalmological examination performed. Ophthalmic examination should be carried out at periodic intervals in any patients receiving this drug for an extended period of time.

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 nonsteroidal 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. KETOPROFEN 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. KETOPROFEN should not be administered within 12 hours of methotrexate infusion.

Acetylsalicylic Acid: Concurrent administration of acetylsalicylic acid (ASA) decreased ketoprofen

protein binding and increased its plasma clearance. The overall result was a 40% reduction in the AUC of ketoprofen. KETOPROFEN does not alter ASA absorption.

Oral anticoagulants: Ketoprofen 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 20 patients undergoing therapy with coumadin and simultaneously receiving ketoprofen, failed to demonstrate potentiation of anticoagulant effect. Nevertheless, close monitoring of patients is recommended when KETOPROFEN is given concomitantly with anticoagulants.

Diuretics: Hydrochlorothiazide, given concomitantly with ketoprofen 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.

Antacids: Concomitant administration of magnesium hydroxide and aluminum 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 KETOPROFEN is co-administered 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. KETOPROFEN is not recommended in association with probenecid.

Ketoprofen 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 Tests

The presence of ketoprofen 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.

Ketoprofen 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.

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 on occasion, particularly in the elderly.

In clinical trials of ketoprofen involving 1,542 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 1,076 patients; however, in open label continuation studies in 1,292 patients the rate was greater than 2%.

The detailed breakdown of side effects with their corresponding frequencies (not indicated when <1%) is given herewithin. 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.

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.

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

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

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

Hematological: 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 ketoprofen 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 (doses up to 5000 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

The usual dosage for KETOPROFEN capsules or 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.

Patients with rheumatoid arthritis or osteoarthritis on a maintenance dose of 200 mg/day may be changed to a once daily dose of KETOPROFEN SR 200 mg tablets administered in the morning or evening. KETOPROFEN SR tablets should be swallowed whole.

KETOPROFEN-E and KETOPROFEN SR tablets provide alternative presentations for those who may prefer these dosage forms. No difference in toxicity profile was documented.

The total daily dose of KETOPROFEN capsules or tablets 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 200 mg may be used, but a dose of 300 mg/day should not be exceeded.

Primary dysmenorrhea and mild to moderate pain

The usual dose for KETOPROFEN is 25 to 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

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

INFORMATION TO THE PATIENT

The following text will be dispensed with this drug:

KETOPROFEN

Ketoprofen Capsules and Tablets

Ketoprofen (kee-toe-PROE-fen) which has been prescribed to you by your doctor, is one of a large group of nonsteroidal anti-inflammatory drugs (NSAIDs) 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 and other body reactions.

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

HOW TO USE THIS MEDICINE

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

Be sure to take KETOPROFEN 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 KETOPROFEN enteric-coated tablets (KETOPROFEN-E) or KETOPROFEN

sustained-release tablets (KETOPROFEN SR), 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 them.

If you are taking KETOPROFEN capsules, take them immediately after a meal or with food to lessen stomach upset. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

IF YOU MISS A DOSE

If you miss a dose of KETOPROFEN capsules or 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.

If you take KETOPROFEN SR tablets once a day and if you miss a dose and remember within 8 hours, take it right away and then resume your regular dosing schedule. NEVER DOUBLE DOSES.

IMPORTANT NOTICE

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking KETOPROFEN 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.

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

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

ALWAYS REMEMBER

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

- are allergic to KETOPROFEN or other related medicines of the NSAID group such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin;
- have a history of stomach upset, ulcers, or liver or kidney diseases;
- are pregnant or intend to become pregnant while taking this medication;

- are breast feeding;
- are taking any other medication (either prescription or non-prescription);
- have any other medical problem

While taking this medication:

- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;
- be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;
- check with your doctor if you are not getting any relief or if any problems develop;
- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.

Your regular medical checkups are essential.

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

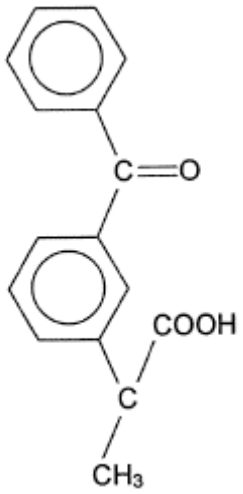
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: ketoprofen

Chemical Name: m-benzoylhydratropic acid

Structural Formula:



Molecular Formula: $C_{16}H_{14}O_3$

Molecular Weight: 254.3

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

Composition

KETOPROFEN capsules each contain 50 mg of ketoprofen. In addition to the active ingredient ketoprofen, each capsule contains the non-medicinal ingredients lactose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, gelatin, sodium lauryl sulfate, FD&C yellow #6, D&C yellow #10, FD&C green #3 and titanium dioxide. The capsule is imprinted with edible red ink.

KETOPROFEN-E enteric-coated tablets contain 50 or 100 mg of ketoprofen. In addition to the active ingredient ketoprofen, each enteric-coated tablet contains the non-medicinal ingredients colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10, dextrates, guar gum, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer dispersion, methylcellulose, polyethylene glycol, sunset yellow supra, talc, titanium dioxide and triethyl citrate.

KETOPROFEN SR tablets contain 200 mg of ketoprofen. In addition to the active ingredient ketoprofen, each sustained-release tablet contains the non-medicinal ingredients dextrates, hydroxypropyl methylcellulose, magnesium stearate, colloidal silicon dioxide, hydroxypropyl cellulose, polyethylene glycol, polyvinyl acetate phthalate, titanium dioxide, stearic acid, triethyl citrate and methanol.

Stability and Storage Recommendations

Store at a controlled room temperature 15-30ºC (59-86ºC). Protect unit dose packages from light.

AVAILABILITY OF DOSAGE FORMS

KETOPROFEN 50 mg capsules are dark green and ivory hard gelatin capsules available in bottles of 100, 500 and 1000.

KETOPROFEN-E 50 mg tablets are round, biconvex, yellow, enteric-coated tablets engraved “50” on one side. Available in bottles of 100, 500 and 1000.

KETOPROFEN-E 100 mg tablets are round, biconvex, yellow, enteric-coated tablets engraved “100” on one side. Available in bottles of 100, 500 and 1000.

KETOPROFEN SR 200 mg tablets are round, biconvex, white, enteric-coated tablets, engraved “200” on one side. Available in bottles of 100 and 500, and unit dose packages of 100 (10x10).

PHARMACOLOGY

Anti-inflammatory Activity

In the carrageenan-induced rat paw edema test for anti-inflammatory activity, inhibition of edema became significant at 3 mg/kg per os and reached 50% inhibition at 9 mg/kg.

In the carrageenan abscess test in the rat the ED_{50} for ketoprofen was 1.4 mg/kg (0.4-4.0)p.o., and in the guinea pig U.V. erythema test, the ED_{50} was 7.5 mg/kg (3.7-15.0) per os.

In the adjuvant arthritis test in the rat, ketoprofen shows significant activity from a daily dose of 2.5 mg/kg p.o. Ketoprofen at a daily dose of 10 mg/kg orally was well tolerated by polyarthritic rats, and the inhibitory effect on the arthritis was around 70%.

In Selye's granulomatous pouch in the rat, ketoprofen at a dose of 12 mg/kg p.o. over 7 days reduced the pouch by 15.6% and reduced the hemorrhagic exudate by 36.7%. In the asbestos pellet-induced granuloma in the rat, a dose of 15 mg/kg p.o. of ketoprofen caused an average reduction of 19.2% in the granuloma.

Analgesic Activity

In the mouse, analgesic properties of oral ketoprofen were manifested by an effect on the visceral pain induced by phenylbenzoquinone. In this test the ED_{50} was 2.3 mg/kg (1.6-4.5) p.o. In the rat, against pain induced by pressure applied to an inflamed paw (Randall and Selitto test), the ED_{50} of ketoprofen was 2.4 mg/kg (0.8-7.2) p.o.

Antipyretic Activity

In the hyperthermia induced by brewer's yeast in rats, ketoprofen, orally, 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 effect in normal rats and rabbits.

Antibradykinin Activity

Ketoprofen exerts a strong antibradykinin effect. In guinea pigs with bradykinin-induced bronchoconstriction the ED_{50} of ketoprofen was 0.025 mg/kg I.V., and against the bradykinin-induced visceral pain in the mouse, the ED_{50} of ketoprofen was 6.2 mg/kg p.o.

Inhibition of Prostaglandin Synthesis

In the isolated guinea pig lung, ketoprofen exerted a marked inhibitory effect on the biosynthesis of prostaglandins with arachidonic acid as substrate. In this system the EC_{50} for ketoprofen was 0.002 mg/L.

Ketoprofen has been found to be a potent drug in depressing edema in the rat's paw induced by carrageenan, and simultaneously of inhibiting the increased prostaglandin synthesis induced by carrageenan. Ketoprofen also inhibited, in vitro, the synthesis of PGE_2 and PGF_2 from arachidonic acid.

Inhibition of Platelet Aggregation

Ketoprofen inhibits platelet aggregation in vitro in a dose-related manner when the inducer of platelet aggregation is collagen, ADP or adrenaline. The inhibitory effect of ketoprofen is greater than that of indomethacin. This in vitro test involves the same biological phenomena as those occurring in vivo.

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. Absorption is rapid after administration of the drug as an oral capsule 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-release 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 capsule doses, the mean C_{max} of 4.1 mg/L occurs 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 aluminum and magnesium hydroxide antacid or an aluminum 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-calorie meal (approximately 3000 calories/day)

was associated with lower ketoprofen bioavailability values (about 20%) than a low-fat/low-calorie content (approximately 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) is 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 negligible.

Following the administration of capsules or enteric-coated tablets, 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 patients with reduced renal function. In a group of patients with creatinine clearance of 20-60 mL/min., 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

LD_{50} (and 95% probability level exclusive of the 20% confidence limits) mg/kg.

Species	Sex	Oral
Mice *	F	320 (209.0-490.0)
	M	198 (150.0-261.0)
	Combined	221 (187.0-261.1)
Rats **	F	109 (84-141)
	M	109 (84-141)
	Combined	109 (91-131)

* 12 groups, each with 5 animals/sex were treated with the test article (ketoprofen) at logarithmically spaced doses.

** 9 groups, each with 5 animals/sex were treated with the test article (ketoprofen) at logarithmically spaced doses.

Mortality generally occurred within a 6 day period post-dosing in mice, and over a 12 day period in rats.

In mice, pharmacotoxicity was generally characterized by decreased activity, muscle tone and reflexes, ataxia, piloerection, hunchback, and paleness or cyanosis.

In rats, pharmacotoxicity was generally characterized by piloerection, ptosis, paleness, emaciation, epistaxis, decreased activity and reflexes, cyanosis, hunchback, diarrhea, decreased muscle tone, ataxia, and coma.

Necropsy of animals succumbing during the study generally demonstrated pale or dark liver, mild to severe irritation and/or hemorrhage of the small intestine, distended small intestine, pale stomach with severe irritation or hemorrhage, distended stomach, pale or dark spleen and pale or dark kidneys.

Animals sacrificed upon completion of the study showed no pathological findings in mice but red ascites, distention of the stomach and apparent enlargement of the spleen were seen in rats.

Subacute Toxicity

The subacute oral LD_{50} for ketoprofen in the mouse and rat was 180 mg/kg/day and 21 mg/kg/day, respectively, based on treatment for 5 consecutive days.

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, hyperfibrinemia 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 6 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 12 animals receiving 27 mg/kg, the first sacrificed after 26 weeks, 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}B1/6/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.

Ulcerogenic Activity

In fasting rats, ketoprofen, at dosages of 4 and 8 mg/kg p.o. for 4 days was comparable in terms of ulcerogenic activity to indomethacin 2 and 4 mg/kg p.o. Ketoprofen 1 and 2 mg/kg p.o. had no effect on the gastrointestinal mucosa.

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 9 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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