CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74879

DRAFT FINAL PRINTED LABELING

SCHEIN
PHARMACEUTICAL

NDC 0364-2667-01 100 Capsules

KETOPROFEN
Extended-release Capsules

200 mg

DEC 10

Caution: Federal law prohibits dispensing without prescription

Each extended-release capsule contains:
Ketoprofen, USP, 200 mg

Usual dosage: 1 capsule daily. See accompanying literature.

Dispense in a tight container, as defined in the USP, with a child-resistant closure as required.

STORE AT CONTROLLED ROOM TEMPERATURE
20°-25°C (68°-77°F).

Keep tightly closed.

Mfd. for: Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

Mfd. by: *elan pharma ltd.*
Athlone, County Westmeath, Ireland

A-B

N 3 0364-2667-01 4

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2667-05 500 Capsules

KETOPROFEN
Extended-release Capsules

DEC 10

200 mg

Caution: Federal law prohibits dispensing without prescription

Each extended-release capsule contains:
Ketoprofen, USP, 200 mg

Usual dosage: 1 capsule daily. See accompanying literature.

Dispense in a tight container, as defined in the USP, with a child-resistant closure as required.

STORE AT CONTROLLED ROOM TEMPERATURE
20°-25°C (68°-77°F).

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N 3 0364-2667-05 2

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2667-05 500 Capsules

KETOPROFEN
Extended-release Capsules

200 mg

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Each extended-release capsule contains:
Ketoprofen, USP, 200 mg

Usual dosage: 1 capsule daily. See accompanying literature.

Dispense in a tight container, as defined in the USP, with a child-resistant closure as required.

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A-B

N 3 0364-2667-05 2

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2667-02 1000 Capsules

KETOPROFEN
Extended-release Capsules

200 mg

Each extended-release capsule contains:
Ketoprofen, USP, 200 mg

Usual dosage: 1 capsule daily. See accompanying literature.

Dispense in a tight container, as defined in the USP, with a child-resistant closure as required.

STORE AT CONTROLLED ROOM TEMPERATURE
20°-25°C (68°-77°F).

Keep tightly closed.

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B

N 3 0364-2667-02 1

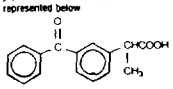
Control Number and Expiration Date

KETOPROFEN
Extended-release Capsules

Revised May 1997

DESCRIPTION

Ketoprofen is a nonsteroidal anti-inflammatory drug. The chemical name for ketoprofen is 2-(3-benzoylphenyl)-propionic acid. The structural formula is represented below:



$C_{16}H_{14}O_3$ MW 254.29

It has a pKa of 5.94 in methanol:water (3:1) and an n-octanol:water partition coefficient of 0.97 (buffer pH 7.4). Ketoprofen is a white or off-white, odorless, nonhygroscopic, fine to granular powder, melting at about 95°C. It is freely soluble in ethanol, chloroform, acetone, ether and soluble in benzene and strong alkali, but practically insoluble in water at 20°C.

Each extended-release capsule, for oral administration, contains 200 mg of ketoprofen in the form of hundreds of coated pellets. The dissolution of the pellets is pH dependent, with optimum dissolution occurring at pH 6.5 to 7.5. There is no dissolution at pH 1.

Ketoprofen extended-release capsules contain the following inactive ingredients: black S-1-8100 HV colloidal silicon dioxide, ethylcellulose, FD&C Blue No. 2, gelatin, isopropyl alcohol (trace amounts), polyvinylpyrrolidone, silicon dioxide, sodium lauryl sulfate, corn starch, sucrose, talc and titanium dioxide.

CLINICAL PHARMACOLOGY

Ketoprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties.

The anti-inflammatory, analgesic, and antipyretic properties of ketoprofen have been demonstrated in classical animal and *in vitro* test systems. In *anti-inflammatory models* ketoprofen has been shown to have inhibitory effects on prostaglandin and leukotriene synthesis, to have antibradykinin activity, as well as to have lysosomal membrane-stabilizing action. However, its mode of action, like that of other nonsteroidal anti-inflammatory drugs, is not fully understood.

Pharmacodynamics

Ketoprofen is a racemate with only the S enantiomer possessing pharmacological activity. The enantiomers have similar concentration time curves and do not appear to interact with one another.

Pharmacokinetics

General

The systemic availability (F_a) when the oral formulation is compared with IV administration is approximately 90% in humans. For 75 mg to 200 mg single doses, the area under the curve has been shown to be dose proportional.

Ketoprofen is >99% bound to plasma proteins, mainly to albumin.

Absorption

Ketoprofen is well-absorbed from this dosage form, although an observable increase in plasma levels does not occur until approximately 2 to 3 hours after taking the formulation. Peak plasma levels are usually reached 6 to 7 hours after dosing. (See Table)

When ketoprofen is administered with food, its total bioavailability (AUC) is not altered, however, the rate of absorption is slowed.

Administration of ketoprofen extended-release capsules with a high-fat meal causes a delay of about 2 hours in reaching the C_{max}, neither the total bioavailability (AUC) nor the C_{max} is affected. Circadian changes in the absorption process have not been studied.

The administration of antacids or other drugs which may raise stomach pH would not be expected to change the rate or extent of absorption of ketoprofen from ketoprofen extended-release capsules.

Multiple dosing

Steady-state concentrations of ketoprofen are attained within 24 hours after commencing treatment with ketoprofen extended-release capsules. In studies with healthy male volunteers, the trough level at 24 hours following administration of ketoprofen extended-release cap-

release capsules with [illegible] causes a delay of about 2 hours in reaching the C_{max}. Neither the total bioavailability, AUC, nor the C_{max} is affected. Circadian changes in the absorption process have not been studied.

The administration of antacids or other drugs which may raise stomach pH would not be expected to change the rate or extent of absorption of ketoprofen from ketoprofen extended release capsules.

Multiple dosing

Steady state concentrations of ketoprofen are attained within 24 hours after commencing treatment with ketoprofen extended release capsules. In studies with healthy male volunteers, the trough level at 24 hours following administration of ketoprofen extended-release capsules was 0.4 mg/L. Relative to the peak plasma concentration, the accumulation of ketoprofen after multiple doses of extended release ketoprofen capsules is minimal.

Pharmacokinetic Parameters[#] for Extended release Ketoprofen Capsules

Kinetic Parameters	Ketoprofen Extended-release Capsules (1 x 200 mg)
Extent of oral absorption (bioavailability) F_1 (%)	~90
Peak plasma levels C_{max} (mg/L)	
Fasted	$3.1_{\pm}1.2$
Fed	$3.4_{\pm}1.3$
Time to peak concentration t_{max} (h)	
Fasted	$6.8_{\pm}2.1$
Fed	$9.2_{\pm}2.6$
Area under plasma concentration-time curve $AUC_{0-2\infty}$ (mg• h/L)	
Fasted	$30.1_{\pm}7.9$
Fed	$31.3_{\pm}8.1$
Oral-dose clearance CL/F (L/h)	$6.8_{\pm}1.8$
Half-life $t_{1/2}$ (h) [See footnote †]	$5.4_{\pm}2.2$

Values expressed are mean ± standard deviation

† In the case of ketoprofen extended-release capsules, absorption is slowed, intrinsic clearance is unchanged, but because the rate of elimination is dependent on absorption, the half-life is prolonged.

Metabolism

The metabolic fate of ketoprofen is glucuronide conjugation to form an unstable acyl-glucuronide. The glucuronic acid moiety can be converted back to the parent compound. Thus, the metabolite serves as a potential reservoir for parent drug, and this may be important in persons with renal insufficiency, whereby the conjugate may accumulate in the serum and undergo deconjugation back to the parent drug (see CLINICAL PHARMACOLOGY *Special Populations*: Renally Impaired). The conjugates are reported to appear only in trace amounts in plasma in healthy adults but are higher in elderly subjects-presumably because of reduced renal clearance. It has been demonstrated that in elderly subjects following multiple doses (50 mg every 6 h), the ratio of conjugated to parent ketoprofen AUC was 30% and 3%, respectively for the S & R enantiomers.

There are no known active metabolites of ketoprofen. Ketoprofen has been shown not to induce drug-metabolizing enzymes.

Elimination

The plasma clearance of ketoprofen is approximately 0.08 L/kg/h with a V_d of 0.1 L/kg after IV administration. The elimination half-life of ketoprofen has been reported to be 2.05 ± 0.58 h (Mean ± S.D.) following IV administration, and from 5.4 ± 2.2 h after administration of ketoprofen extended-release capsules 200 mg. In cases of slow drug absorption, the elimination rate is dependent on the absorption rate and thus $t_{1/2}$ relative to an IV dose appears prolonged.

After a single 200 mg dose of ketoprofen extended-release capsules, the plasma levels decline slowly, and average 0.4 mg/L after 24 hours.

In a 24-hour period approximately 80% of an administered dose of ketoprofen is excreted in the urine, primarily as the glucuronide metabolite.

Enterohepatic recirculation of the drug has been postulated although biliary levels have never been measured to confirm this.

Special Populations

Elderly: Clearance and unbound fraction

The plasma and renal clearance of ketoprofen is reduced in the elderly (mean age, 73 years) compared to a younger normal population (mean age, 27 years). Hence, ketoprofen peak concentration and AUC increase with increasing age. In addition, there is a corresponding increase in unbound fraction with increasing age. Data from one trial suggest that the increase is greater in women than in men. It has not been determined whether age-related changes in absorption among the elderly contribute to the changes in bioavailability of ketoprofen.

The effects of age and gender on ketoprofen disposition were investigated in 2 small studies in which elderly male and female subjects received ketoprofen extended-release capsules. The results were compared with those from another study conducted in healthy young men.

Compared to the younger subject group, the elimination half-life in the elderly was prolonged by 54% and total drug C_{max} and AUC were 40% and 70% higher, respectively. Plasma concentrations in the elderly after single doses and at steady state were essentially the same. Thus, no drug accumulation occurs.

Renally impaired

Studies of the effects of renal-function impairment have been small. They indicate a decrease in clearance in patients with impaired renal function. In 23 patients with renal impairment, free ketoprofen peak concentration was not significantly elevated, but free ketoprofen clearance was reduced from 15 L/kg/h for normal subjects to 7 L/kg/h in patients with mildly impaired renal function, and to 4 L/kg/h in patients with moderately to severely impaired renal function. The elimination $t_{1/2}$ was prolonged from 1.6 hours in normal subjects to approximately 3 hours in patients with mild renal impairment, and to approximately 5 to 9 hours in patients with moderately [illegible]

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No studies have been conducted in patients with renal impairment taking ketoprofen extended-release capsules. It is recommended that only the immediate-release ketoprofen capsules be used to treat patients with significant renal impairment (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**).

Hepatically impaired

For patients with alcoholic cirrhosis, no significant changes in the kinetic disposition of ketoprofen immediate release capsules were observed relative to age-matched normal subjects: the plasma clearance of drug was 0.87 L/kg/h in 26 hepatically impaired patients. The elimination half-life was comparable to that observed for normal subjects. However, the unbound (biologically active) fraction was approximately doubled, probably due to hypoalbuminemia and high variability which was observed in the pharmacokinetics for cirrhotic patients. Therefore, these patients should be carefully monitored and daily doses of ketoprofen kept at the minimum providing the desired therapeutic effect.

No studies have been conducted in patients with hepatic impairment taking ketoprofen extended-release capsules. It is recommended that only immediate-release ketoprofen be used to treat patients who have hepatic impairment and serum albumin levels below 3.5 g/dl. (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**)

Clinical Trials

Rheumatoid Arthritis and Osteoarthritis

The efficacy of ketoprofen has been demonstrated in patients with rheumatoid arthritis and osteoarthritis. Using standard assessments of therapeutic response there were no detectable differences in effectiveness or in the incidence of adverse events in crossover comparison of ketoprofen immediate-release capsules and ketoprofen extended-release capsules. In other trials, ketoprofen demonstrated effectiveness comparable to aspirin, ibuprofen, naproxen, piroxicam, diclofenac, and indomethacin. In some of these studies there were more dropouts due to gastrointestinal side effects among patients on ketoprofen than among patients on other NSAIDs.

In studies with patients with rheumatoid arthritis ketoprofen was administered in combination with gold salts, antimalarials, low-dose methotrexate, d-penicillamine, and/or corticosteroids with results comparable to those seen with control nonsteroidal drugs.

Individualization of Dosage

In patients with significant renal impairment, immediate-release ketoprofen should be used. In elderly patients, renal function may be reduced with apparently normal serum creatinine and/or BUN levels. Therefore, immediate-release ketoprofen capsules are the recommended formulation of ketoprofen.

It is recommended that for patients with impaired liver function and serum albumin concentration less than 3.5 g/dl, immediate-release ketoprofen capsules rather than the extended-release capsules should be used. All patients with metabolic impairment, particularly those with both hypoalbuminemia and reduced renal function, may have increased levels of free (biologically active) ketoprofen and should be closely monitored. The dosage may be increased to the range recommended for the general population, if necessary, only after good individual tolerance has been ascertained.

Because hypoalbuminemia and reduced renal function both increase the fraction of free drug (biologically active form), patients who have both conditions may be at greater risk of adverse effects. Therefore, it is recommended that such patients also be started on lower doses of immediate-release ketoprofen and closely monitored.

As with other nonsteroidal anti-inflammatory drugs, the predominant adverse effects of ketoprofen are gastrointestinal. To attempt to minimize these effects, physicians may wish to prescribe that ketoprofen be taken with antacids, food, or milk. Although food delays the absorption (see **CLINICAL PHARMACOLOGY**), in most of the clinical trials ketoprofen was taken with food or milk.

Physicians may want to make specific recommendations to patients about when they should take ketoprofen in relation to food and/or what patients should do should experience minor GI symptoms.

INDICATIONS AND USAGE

Ketoprofen extended-release capsules are indicated for the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis. Ketoprofen extended-release capsules are not recommended for treatment of acute pain because of their extended-release characteristics (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

CONTRAINDICATIONS

Ketoprofen is contraindicated in patients who have shown hypersensitivity to it. Ketoprofen should not be given to patients in whom aspirin or other non-

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CONTRAINDICATIONS

Ketoprofen is contraindicated in patients who have shown hypersensitivity to it. Ketoprofen should not be given to patients in whom aspirin or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions. Because severe, rarely fatal, anaphylactic reactions to ketoprofen have been reported in such patients.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper-gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of several months to two years' duration, symptomatic upper-GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no other risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

General

Ketoprofen and other nonsteroidal anti-inflammatory drugs cause nephritis in mice and rats associated with chronic administration. Rare cases of interstitial nephritis or nephrotic syndrome have been reported in humans with ketoprofen since it has been marketed.

A second form of renal toxicity has been seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal blood flow. In these patients, administration of a nonsteroidal anti-inflammatory drug results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in renal blood flow which may precipitate overt renal failure. 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 drug therapy is typically followed by recovery to the pretreatment state.

Since ketoprofen is primarily eliminated by the kidneys and its pharmacokinetics are altered by renal failure (see **CLINICAL PHARMACOLOGY**), patients with significantly impaired renal function should be closely monitored and a reduction of dosage should be anticipated to avoid accumulation of ketoprofen and/or its metabolites (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**).

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 disappear with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) 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 a more severe hepatic reaction while on therapy with ketoprofen. Serious hepatic reactions, including jaundice, have been reported from post-marketing experience with ketoprofen as well as with other nonsteroidal anti-inflammatory drugs.

In patients with chronic liver disease with reduced serum albumin levels, ketoprofen's pharmacokinetics are altered (see **CLINICAL PHARMACOLOGY**). Such patients should be closely monitored and a reduction of dosage should be anticipated to avoid high blood levels of ketoprofen and/or its metabolites (see **CLINICAL PHARMACOLOGY Individualization of Dosage**).

If steroid dosage is reduced or eliminated during therapy, it should be reduced slowly and the patients observed close-

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If steroid dosage is reduced or eliminated during therapy, it should be reduced slowly and the patients observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by nonsteroidal anti-inflammatory drugs, which may produce fluid retention or significant gastrointestinal blood loss in some patients. Patients on long-term treatment with NSAIDs, including ketoprofen, should have their hemoglobin or hematocrit checked if they develop signs or symptoms of anemia.

Peripheral edema has been observed in approximately 2% of patients taking ketoprofen. Therefore, as with other nonsteroidal anti-inflammatory drugs, ketoprofen should be used with caution in patients with fluid retention, hypertension, or heart failure.

Information for Patients

Like other drugs of its class, ketoprofen is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS, General**, and **ADVERSE REACTIONS** sections) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Because aspirin causes an increase in the level of unbound ketoprofen, patients should be advised not to take aspirin while taking ketoprofen (see **PRECAUTIONS, Drug Interactions**). It is possible that minor adverse symptoms of gastric intolerance may be prevented by administering ketoprofen capsules with antacids, food, or milk. Ketoprofen extended-release capsules have not been studied with antacids. Because food and milk do affect the rate but not the extent of absorption (see **CLINICAL PHARMACOLOGY**), physicians may want to make specific recommendations to patients about when they should take ketoprofen in relation to food and/or what patients should do if they experience minor GI symptoms associated with ketoprofen therapy.

Laboratory Tests

Serious GI toxicity, such as bleeding, perforation and ulceration of the GI tract, can occur without warning symptoms. Physicians should observe for signs or symptoms of GI ulceration and bleeding, and should inform patients of the importance of this follow-up (see **WARNINGS-Risk of GI Ulceration, Bleeding, and Perforation with NSAID Therapy**).

Drug Interactions

The following drug interactions were studied with ketoprofen doses of 200 mg/day. The possibility of increased interaction should be kept in mind when ketoprofen immediate-release capsule doses greater than 50 mg as a single dose or 200 mg of ketoprofen per day are used concomitantly with highly bound drugs.

1 Antacids

Concomitant administration of magnesium-hydroxide and aluminum hydroxide does not interfere with the rate or extent of the absorption of ketoprofen administered as immediate-release ketoprofen capsules.

2 Aspirin

Ketoprofen does not alter aspirin absorption; however, in a study of 12 normal subjects, concurrent administration of aspirin decreased ketoprofen protein binding and increased ketoprofen plasma clearance from 0.07 L/kg/h without aspirin to 0.11 L/kg/h with aspirin. The clinical significance of these changes has not been adequately studied. Therefore, concurrent use of aspirin and ketoprofen is not recommended.

3 Diuretics

Hydrochlorothiazide given concomitantly with ketoprofen produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients taking diuretics are at a greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition (see **PRECAUTIONS, General**).

4 Digoxin

In a study of 12 patients with congestive heart failure, where ketoprofen and digoxin were concomitantly administered, ketoprofen did not alter the serum levels of digoxin.

5 Warfarin

In a short-term controlled study in 14 normal volunteers, ketoprofen did not significantly interfere with the effect of warfarin on prothrombin time. Bleeding from a number of sites may be a complication of warfarin treatment and GI bleeding a complication of ketoprofen treatment. Because prostaglandins play an important role in hemostasis, and ketoprofen has an effect on platelet function as well (see **PRECAUTIONS, Drug/Laboratory Test Interactions: Effect on Blood Coagulation**), concurrent therapy with ketoprofen and warfarin requires close monitoring of patients on both drugs.

6 Probenecid

Probenecid increases both free and bound ketoprofen by reducing the plasma clearance of ketoprofen to about one-third as well as decreasing its protein binding. Therefore, the combination of ketoprofen and probenecid is not recommended.

7 Methotrexate

Ketoprofen, like other NSAIDs, may cause changes in the elimination of methotrexate leading to elevated serum levels of the drug and increased toxicity.

8 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.

Drug/Laboratory Test Interactions: Effect on Blood Coagulation

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Chronic oral toxicity studies in mice (up to 32 mg/kg/day; 96 mg/m^2/day) did not indicate a carcinogenic potential for ketoprofen. The maximum recommended human therapeutic dose is 300 mg/day for a 60 kg patient with a body surface area of 1.6 m^2, which is 5 mg/kg/day or 185 mg/m^2/day. Thus the mice were treated at 0.5 times the maximum human daily dose based on surface area.

A 2-year carcinogenicity study in rats, using doses up to 6.0 mg/kg/day (36 mg/m^2/day), showed no evidence of tumorigenic potential. All groups were treated for 104 weeks except the females receiving 6.0 mg/kg/day (36 mg/m^2/day) where the drug treatment was terminated in week 81 because of low survival; the remaining rats were sacrificed after week 87. Their survival in the groups treated for 104 weeks was within 6% of the control group. An earlier 2-year study with doses up to 12.5 mg/kg/day (75 mg/m^2/day) also showed no evidence of tumorigenicity, but the survival rate was low and the study was therefore judged inconclusive. Ketoprofen did not show mutagenic potential in the Ames Test. Ketoprofen administered to male rats (up to 9 mg/kg/day; or 54 mg/m^2/day) had no significant effect on reproductive performance or fertility. In female rats administered 6 or 9 mg/kg/day (36 or 54 mg/m^2/day), a decrease in the number of implantation sites has been noted. The dosages of 36 mg/m^2/day in rats represent 0.2 times the maximum recommended human dose of 185 mg/m^2/day (see above).

Abnormal spermatogenesis or inhibition of spermatogenesis developed in rats and dogs at high doses, and a decrease in the weight of the testes occurred in dogs and baboons at high doses.

Teratogenic Effects: Pregnancy Category B

In teratology studies ketoprofen administered to mice at doses up to 12 mg/kg/day (36 mg/m^2/day) and rats at doses up to 9 mg/kg/day (54 mg/m^2/day), the approximate equivalent of 0.2 times the maximum recommended therapeutic dose of 185 mg/m^2/day showed no ter-

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There are no adequate and well-controlled studies in pregnant women. Because animal teratology studies are not always predictive of the human response, ketoprofen should be used during pregnancy only if the potential benefit justifies the risk.

Labor and Delivery

The effects of ketoprofen on labor and delivery in pregnant women are unknown. Studies in rats have shown ketoprofen at doses of 6 mg/kg (36 mg/m²/day, approximately equal to 0.2 times the maximum recommended human dose) prolongs pregnancy when given before the onset of labor. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of ketoprofen during late pregnancy should be avoided.

Nursing Mothers

Data on secretion in human milk after ingestion of ketoprofen do not exist. In rats, ketoprofen at doses of 9 mg/kg (54 mg/m²/day, approximately 0.3 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. As with other drugs that are excreted in milk, ketoprofen is not recommended for use in nursing mothers.

Pediatric Use

Ketoprofen is not recommended for use in pediatric patients, because its safety and effectiveness have not been studied in the pediatric population.

ADVERSE REACTIONS

The incidence of common adverse reactions (above 1%) was obtained from a population of 835 immediate-release ketoprofen treated patients in double-blind trials lasting from 4 to 54 weeks and in 422 patients treated with ketoprofen extended-release capsules in trials lasting from 4 to 16 weeks.

Minor gastrointestinal side effects predominated; upper gastrointestinal symptoms were more common than lower gastrointestinal symptoms. In crossover trials in 321 patients with rheumatoid arthritis or osteoarthritis, there was no difference in either upper or lower gastrointestinal symptoms between patients treated daily with 200 mg of ketoprofen extended-release capsules or 75 mg of immediate-release ketoprofen t.i.d. (225 mg/day). Peptic ulcer or GI bleeding 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 incidence of peptic ulceration in patients on NSAIDs is dependent on many risk factors including age, sex, smoking, alcohol use, diet, stress, concomitant drugs such as aspirin and corticosteroids, as well as the dose and duration of treatment with NSAIDs (see **WARNINGS**).

Gastrointestinal reactions were followed in frequency by central nervous system side effects, such as headache, dizziness, or drowsiness. The incidence of some adverse reactions appears to be dose-related (see **DOSAGE AND ADMINISTRATION**). Rare adverse reactions (incidence less than 1%) were collected from foreign reports to manufacturers and regulatory agencies, publications, and U.S. clinical trials.

Reactions are listed below under body system, then by incidence or number of cases in decreasing incidence.

Incidence Greater Than 1% (Probable Causal Relationship)

Digestive: Dyspepsia (11%), nausea*, abdominal pain*, diarrhea*, constipation*, flatulence*, anorexia, vomiting, stomatitis.

Nervous System: Headache*, dizziness, CNS inhibition (i.e., pooled reports of somnolence, malaise, depression, etc.) or excitation (i.e., insomnia, nervousness, dreams, etc.)*.

Special Senses: Tinnitus, visual disturbance.

Skin and Appendages: Rash.

Urogenital: Impairment of renal function (edema, increased BUN)*, signs or symptoms of urinary-tract irritation.

*Adverse events occurring in 3 to 9% of patients.

Incidence Less Than 1% (Probable Causal Relationship)

Body as a Whole: Chills, facial edema, infection, pain, allergic reaction, anaphylaxis.

Cardiovascular: Hypertension, palpitation, tachycardia, congestive heart failure, peripheral vascular disease, vasodilation.

Digestive: Appetite increased, dry mouth, eructation, gastritis, rectal hemorrhage, melena, fecal occult blood, salivation, peptic ulcer, gastrointestinal perforation, hematemesis, intestinal ulceration.

Hemic: Hypocoagulability, agranulocytosis, anemia, hemolysis, purpura, thrombocytopenia.

Metabolic and Nutritional: Thirst, weight gain, weight loss, hepatic dysfunction, hyponatremia.

Musculoskeletal: Myalgia.

Nervous System: Amnesia, confusion, impotence, migraine, paresthesia, vertigo.

Respiratory: Dyspnea, hemoptysis, epistaxis, pharyngitis, rhinitis, bronchospasm, laryngeal edema.

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Musculoskeletal Myalgia

Nervous System Amnesia, confusion, impotence, migraine, paresthesia, vertigo

Respiratory Dyspnea, hemoptysis, epistaxis, pharyngitis, rhinitis, bronchospasm, laryngeal edema

Skin and Appendages Alopecia, eczema, pruritus, purpuric rash, sweating, urticaria, bullous rash, exfoliative dermatitis, photosensitivity, skin discoloration, onycholysis

Special Senses Conjunctivitis, conjunctivitis sicca, eye pain, hearing impairment, retinal hemorrhage and pigmentation change, taste perversion

Urogenital Menometrorrhagia, hematuria, renal failure, interstitial nephritis, nephrotic syndrome

Incidence Less Than 1% (Causal Relationship Unknown)

The following rare adverse reactions, whose causal relationship to ketoprofen is uncertain, are being listed to serve as alerting information to the physician

Body as a Whole *Septicemia, shock*

Cardiovascular Arrhythmias, myocardial infarction

Digestive Buccal necrosis, ulcerative colitis, microvesicular steatosis, jaundice, pancreatitis

Endocrine Diabetes mellitus (aggravated)

Nervous System Dysphoria, hallucination, libido disturbance, nightmares, personality disorder, aseptic meningitis

Urogenital Acute tubulopathy, gynecomastia

OVERDOSAGE

Signs and symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Respiratory depression, coma, or convulsions have occurred following large ketoprofen overdoses. Gastrointestinal bleeding, hypotension, hypertension, or acute renal failure may occur, but are rare.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients with symptoms seen within 4 hours (longer for sustained-release products) or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults; 1 to 2 g/kg in children) with a saline cathartic or sorbitol added to the first dose. Forced diuresis, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to ketoprofen's high protein binding.

Case reports include twenty-six overdoses: 6 were in children, 16 in adolescents, and 4 in adults. Five of these patients had *minor symptoms* (*vomiting* in 4, drowsiness in 1 child). A 12-year-old girl had tonic-clonic convulsions 1 to 2 hours after ingesting an unknown quantity of ketoprofen and 1 or 2 tablets of acetaminophen with hydrocodone. Her ketoprofen level was 1128 mg/L (56 times the upper therapeutic level of 20 mg/L) 3 to 4 hours post-ingestion. Full recovery ensued 18 hours after ingestion following management with intubation, diazepam, and activated charcoal. A 45-year-old woman ingested twelve 200 mg ketoprofen extended-release capsules and 375 mL vodka, was treated with emesis and supportive measures 2 hours after ingestion, and recovered completely with her only complaint being mild epigastric pain.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis and Osteoarthritis

The recommended starting dose of extended-release ketoprofen in otherwise healthy patients is 200 mg administered once a day. A small dose should be utilized initially in small individuals, in debilitated or elderly patients. Immediate-release ketoprofen capsules *are recommended* for *initial dosage* titration and extended-release capsules are recommended for chronic treatment of those patients whose optimum dose is 200 mg/day. The recommended maximum daily dose of ketoprofen is 300 mg. (See **CLINICAL PHARMACOLOGY Individualization of Dosage**)

During titration with immediate-release ketoprofen capsules, if minor side effects appear, they may disappear at a lower dose which may still have an adequate therapeutic effect. If well tolerated but not optimally effective, the dosage may be increased. Individual patients may show a better response to 300 mg daily as compared to 200 mg, although in well-controlled clinical trials patients on 300 mg did not show greater mean effectiveness. They did, however, show an increased frequency of upper- and lower-GI distress and headaches. It is of interest that women also had an increased frequency of these adverse effects compared to men. When treating patients with 300 mg/day, the physician should observe sufficient increased clinical benefit to offset potential increased risk. Dosages higher than 300 mg/day are not recommended because they have not been adequately studied. Relatively smaller people may need smaller doses. (See **CLINICAL PHARMACOLOGY Individualization of Dosage**)

HOW SUPPLIED

Ketoprofen Extended-release Capsules 200 mg, are powder blue opaque/white opaque capsules marked "KETOPROFEN *ER* 200 mg" on one *capsule half* and "SHN" on the other half, supplied in bottles of 100 (NDC 0364-2667-01), 500 (NDC 0364-2667-05) and 1000 (NDC 0364-2667-02).

Dispense in a tight container as defined in the USP with a child-resistant closure as required.

Store at controlled room temperature [illegible]

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Dispense in a tight container as defined in the USP, with a child-resistant closure as required.

Store at controlled room temperature 20°-25°C (68°-77°F).

Keep tightly closed.

Caution: Federal law prohibits dispensing without prescription.

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