

**KETOPROFEN- ketoprofen capsule, extended release**  
**Mylan Pharmaceuticals Inc.**

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**Cardiovascular Thrombotic Events**

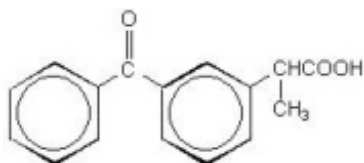
- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (see WARNINGS and PRECAUTIONS).
- Ketoprofen extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (see CONTRAINDICATIONS and WARNINGS).

**Gastrointestinal Risk**

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events (see WARNINGS).

**DESCRIPTION**

Ketoprofen is a nonsteroidal anti-inflammatory drug. The chemical name for ketoprofen is ( $\pm$ )-*m*-Benzoylhydratropic acid with the following structural formula:



Its molecular formula is C<sub>16</sub>H<sub>14</sub>O<sub>3</sub>, with a molecular weight of 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, USP 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 ketoprofen extended-release capsule, USP for oral administration contains 200 mg of ketoprofen, USP. In addition, each capsule contains the following inactive ingredients: ammonium hydroxide, black iron oxide, colloidal anhydrous silica, dibutyl sebacate, ethylcellulose, FD&C Blue No. 2, gelatin, hypromellose, maltodextrin, methacrylic acid

copolymer type B, oleic acid, polyacrylate dispersion, silicon dioxide, sodium lauryl sulfate, sugar spheres, talc, titanium dioxide, triacetin, triethyl citrate and yellow iron oxide.

In addition, the black imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac glaze.

## **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.

An analgesic effect-concentration relationship for ketoprofen was established in an oral surgery pain study with ketoprofen capsules. The effect-site rate constant ( $K_{e0}$ ) was estimated to be  $0.9 \text{ hour}^{-1}$  (95% confidence limits: 0 to 2.1), and the concentration ( $C_{e50}$ ) of ketoprofen that produced one-half the maximum PID (pain intensity difference) was 0.3 mcg/mL (95% confidence limits: 0.1 to 0.5). Thirty-three (33) to 68% of patients had an onset of action (as measured by reporting some pain relief) within 30 minutes following a single oral dose in postoperative pain and dysmenorrhea studies. Pain relief (as measured by remedication) persisted for up to 6 hours in 26 to 72% of patients in these studies.

### **Pharmacokinetics**

#### **General**

Ketoprofen extended-release capsules contain ketoprofen. They differ only in their release characteristics. Ketoprofen capsules release drug in stomach whereas ketoprofen extended-release capsules are designed to resist dissolution in the low pH of gastric fluid but release drug at a controlled rate in the higher pH environment of the small intestine (see DESCRIPTION).

Irrespective of the pattern of release, the systemic availability ( $F_s$ ) when either oral formulation is compared with IV administration is approximately 90% in humans. For 75 to 200 mg single doses, the area under the curve has been shown to be dose proportional. The figure depicts the plasma time curves associated with both products.

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

Separate sections follow which delineate differences between ketoprofen capsules and ketoprofen extended-release capsules.

### ***Absorption***

Ketoprofen capsules are rapidly and well-absorbed, with peak plasma levels occurring within 0.5 to 2 hours.

Ketoprofen extended-release capsules are also 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 Figure and Table, below).

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

Ketoprofen capsules – Food intake reduces  $C_{max}$  by approximately one-half and increases the mean time to peak concentration ( $t_{max}$ ) from 1.2 hours for fasting subjects (range, 0.5 to 3 hours) to 2.0 hours for fed subjects (range, 0.75 to 3 hours). The fluctuation of plasma peaks may also be influenced by circadian changes in the absorption process.

Concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with absorption of ketoprofen capsules.

Ketoprofen extended-release capsules – 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 extended-release capsules.

### ***Multiple Dosing***

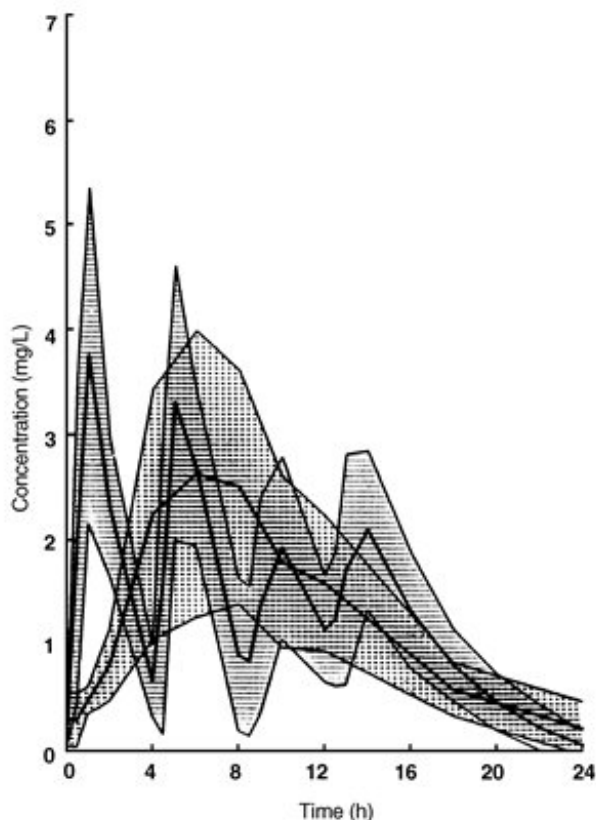
Steady-state concentrations of ketoprofen are attained within 24 hours after commencing treatment with ketoprofen extended-release capsules. In studies with healthy male volunteers, trough levels at 24 hours following administration of ketoprofen 200 mg extended-release capsules were 0.4 mg/L compared with 0.07 mg/L at 24 hours following administration of ketoprofen 50 mg capsules QID (12 hours), or 0.13 mg/L following administration of ketoprofen 75 mg capsules TID for 12 hours. Thus, relative to the peak plasma concentration, the accumulation of ketoprofen after multiple doses of ketoprofen extended-release capsules is minimal.

The figure below shows a reduction in peak height and area after the second 50 mg dose. This is probably due to a combination of food effects, circadian effects, and plasma sampling times. It is unclear to what extent each factor contributes to the loss of peak height and area.

The shaded area represents  $\pm 1$  standard deviation (S.D.) around the mean for ketoprofen capsules or ketoprofen extended-release capsules.

## **KETOPROFEN PLASMA CONCENTRATIONS IN SUBJECTS RECEIVING 200 MG OF**

**KETOPROFEN EXTENDED-RELEASE CAPSULES ONCE A DAY (QD), OR 50 MG OF KETOPROFEN CAPSULES EVERY 4 HOURS FOR 16 HOURS**



**COMPARISON OF PHARMACOKINETIC PARAMETERS\* FOR KETOPROFEN CAPSULES AND KETOPROFEN EXTENDED-RELEASE CAPSULES**

Kinetic Parameters	Ketoprofen Immediate-Release (4 x 50 mg)	Ketoprofen Extended-Release (1 x 200 mg)
Extent of oral absorption (bioavailability) $F_s$ (%)	~ 90	~ 90
Peak plasma levels $C_{max}$ (mg/L)		
Fasted	3.9 ± 1.3	3.1 ± 1.2
Fed	2.4 ± 1.0	3.4 ± 1.3
Time to peak concentration $t_{max}$ (h)		
Fasted	1.2 ± 0.6	6.8 ± 2.1
Fed	2.0 ± 0.8	9.2 ± 2.6
Area under plasma concentration-time curve $AUC_{0-24h}$ (mg•h/L)		
Fasted	32.1 ± 7.2	30.1 ± 7.9
Fed	36.6 ± 8.1	31.3 ± 8.1
Oral-dose clearance $CL/F$ (L/h)	6.9 ± 0.8	6.8 ± 1.8

Half-life $t_{1/2}$ (h)	2.1 ± 1.2	5.4 ± 2.2
[See footnote †]		

\* 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  $2.05 \pm 0.58$  h (Mean ± S.D.) following IV administration, from 2 to 4 h following administration of ketoprofen capsules, and  $5.4 \pm 2.2$  h after administration of ketoprofen 200 mg extended-release capsules. 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 (see Figure above).

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 (see PRECAUTIONS: Geriatric Use).

**Ketoprofen capsules** – In a study conducted with young and elderly men and women, results for subjects older than 75 years of age showed that free drug AUC increased by 40% and  $C_{max}$  increased by 60% as compared with estimates of the same parameters in young subjects (those younger than 35 years of age; see DOSAGE AND ADMINISTRATION).

Also in the elderly, the ratio of intrinsic clearance/availability decreased by 35% and plasma half-life was prolonged by 26%. This reduction is thought to be due to a decrease in hepatic extraction associated with aging.

**Ketoprofen extended-release capsules** – The effects of age and gender on ketoprofen disposition were investigated in 2 small studies in which elderly male and female subjects received ketoprofen 200 mg 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.

In comparison to younger subjects taking the ketoprofen immediate-release formulation, there was a decrease of 16% and 25% in total drug  $C_{max}$  and AUC, respectively, among the elderly. Free drug data are not available for ketoprofen extended-release capsules.

### ***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 to severely impaired renal function.

No studies have been conducted in patients with renal impairment taking ketoprofen extended-release capsules (see DOSAGE AND ADMINISTRATION).

### ***Hepatically Impaired***

For patients with alcoholic cirrhosis, no significant changes in the kinetic disposition of ketoprofen capsules were observed relative to age-matched normal subjects: the plasma clearance of drug was 0.07 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 (see DOSAGE AND ADMINISTRATION).

## **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 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.

### ***Management of Pain***

The effectiveness of ketoprofen capsules 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. Doses larger than 25 mg generally could not be shown to be 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. Studies in postoperative pain have shown that ketoprofen capsules in doses of 25 to 100 mg was comparable to 650 mg of acetaminophen with 60 mg of codeine, or 650 mg of acetaminophen with 10 mg of oxycodone. Ketoprofen tended to be somewhat slower in onset; peak pain relief was about the same and the duration of the effect tended to be 1 to 2 hours longer, particularly with the higher doses of ketoprofen.

The use of ketoprofen extended-release capsules in patients with acute pain is not recommended, since, in comparison to ketoprofen capsules, ketoprofen extended-release capsules would be expected to have a delayed analgesic response due to its extended-release characteristics.

## **INDICATIONS AND USAGE**

Carefully consider the potential benefits and risks of ketoprofen extended-release capsules before deciding to use ketoprofen extended-release capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

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 its extended-release characteristics (see CLINICAL PHARMACOLOGY:

Pharmacokinetics).

## **CONTRAINDICATIONS**

Ketoprofen extended-release capsules are contraindicated in patients who have shown hypersensitivity to ketoprofen.

Ketoprofen extended-release capsules should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic reactions to ketoprofen have been reported in such patients (see WARNINGS: Anaphylactoid Reactions and PRECAUTIONS: General: Preexisting Asthma).

Ketoprofen extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

## **WARNINGS**

### **Cardiovascular Effects**

#### ***Cardiovascular Thrombotic Events***

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as ketoprofen, increases the risk of serious gastrointestinal (GI) events (see WARNINGS).

#### ***Status Post Coronary Artery Bypass Graft (CABG) Surgery***

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG (see CONTRAINDICATIONS).

#### ***Post-MI Patients***



Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next 4 years of follow-up.

Avoid the use of ketoprofen extended-release capsules in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ketoprofen extended-release capsules are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

### ***Hypertension***

NSAIDs, including ketoprofen extended-release capsules, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ketoprofen extended-release capsules, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

### ***Heart Failure and Edema***

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of ketoprofen may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)] (see Drug Interactions).

Avoid the use of ketoprofen extended-release capsules in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ketoprofen extended-release capsules are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

### ***Gastrointestinal Effects***

#### ***Risk of Ulceration, Bleeding, and Perforation***

NSAIDs, including ketoprofen extended-release capsules, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI

adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

## **Renal Effects**

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory 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, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greater risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

## **Advanced Renal Disease**

No information is available from controlled clinical studies regarding the use of ketoprofen extended-release capsules in patients with advanced renal disease. Therefore, treatment with ketoprofen extended-release capsules is not recommended in these patients with advanced renal disease. If ketoprofen extended-release capsules therapy must be initiated, close monitoring of the patient's renal function is advisable.

## **Anaphylactoid Reactions**

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ketoprofen extended-release capsules. Ketoprofen extended-release capsules should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or

other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS: General: Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

## **Skin Reactions**

NSAIDs, including ketoprofen extended-release capsules, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

## **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ketoprofen extended-release capsules. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ketoprofen extended-release capsules and evaluate the patient immediately.

## **Fetal Toxicity**

### ***Premature Closure of Fetal Ductus Arteriosus***

Avoid use of NSAIDs, including ketoprofen extended-release capsules, in pregnant women at about 30 weeks gestation and later. NSAIDs including ketoprofen extended-release capsules, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

### ***Oligohydramnios/Neonatal Renal Impairment***

Use of NSAIDs, including ketoprofen extended-release capsules, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ketoprofen extended-release capsules use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ketoprofen

extended-release capsules treatment extends beyond 48 hours. Discontinue ketoprofen extended-release capsules if oligohydramnios occurs and follow up according to clinical practice (see PRECAUTIONS: Pregnancy).

## **PRECAUTIONS**

### **General**

Ketoprofen extended-release capsules cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

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.

The pharmacological activity of ketoprofen extended-release capsules in reducing [fever and] inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

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 DOSAGE AND ADMINISTRATION).

### ***Hepatic Effects***

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including ketoprofen extended-release capsules. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal

outcomes have been reported.

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 extended-release capsules. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ketoprofen extended-release capsules should be discontinued.

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 DOSAGE AND ADMINISTRATION).

### ***Hematological Effects***

Anemia is sometimes seen in patients receiving NSAIDs, including ketoprofen extended-release capsules. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including ketoprofen extended-release capsules, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving ketoprofen extended-release capsules who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

### ***Preexisting Asthma***

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, ketoprofen extended-release capsules should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

### **Information For Patients**

**Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.**

1. **Cardiovascular Thrombotic Events:** Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately (see WARNINGS).
2. Ketoprofen extended-release capsules, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding

can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see WARNINGS: Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation).

3. **Serious Skin Reactions, including DRESS:** Advise patients to stop taking ketoprofen extended-release capsules immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible (see WARNINGS).
4. **Heart Failure and Edema:** Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur (see WARNINGS).
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).
7. **Fetal Toxicity:** Inform pregnant women to avoid use of ketoprofen extended-release capsules and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with ketoprofen extended-release capsules is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours (see WARNINGS: Fetal Toxicity, PRECAUTIONS: Pregnancy).

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) 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). 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**

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile checked

periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, ketoprofen extended-release capsules should be discontinued.

## **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 doses greater than 50 mg as a single dose or 200 mg of ketoprofen per day are used concomitantly with highly bound drugs.

### ***ACE Inhibitors***

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

### ***Antacids***

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

### ***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 is not known; however, as with other NSAIDs, concomitant administration of ketoprofen and aspirin is not generally recommended because of the potential of increased adverse effects.

### ***Diuretics***

NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. 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). During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS: Renal Effects), as well as to assure diuretic efficacy.

### ***Digoxin***

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

### ***Lithium***

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to

inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

### ***Methotrexate***

Ketoprofen, like other NSAIDs, may cause changes in the elimination of methotrexate leading to elevated serum levels of the drug and increased toxicity. NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

### ***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.

### ***Warfarin***

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. 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.

## **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<sup>2</sup>/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<sup>2</sup>, which is 5 mg/kg/day or 185 mg/m<sup>2</sup>/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<sup>2</sup>/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<sup>2</sup>/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<sup>2</sup>/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<sup>2</sup>/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<sup>2</sup>/day), a decrease in the number of implantation sites has been noted. The dosages of 36 mg/m<sup>2</sup>/day in rats represent 0.2 times the maximum recommended human dose of 185 mg/m<sup>2</sup>/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.

## **Pregnancy**

### ***Risk Summary***

Use of NSAIDs, including ketoprofen extended-release capsules, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of ketoprofen extended-release capsules use between about 20 and 30 weeks of gestation, and avoid ketoprofen extended-release capsules use at about 30 weeks of gestation and later in pregnancy (see WARNINGS: Fetal Toxicity).

#### *Premature Closure of Fetal Ductus Arteriosus*

Use of NSAIDs, including ketoprofen extended-release capsules, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

#### *Oligohydramnios/Neonatal Renal Impairment*

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, ketoprofen administered to mice at doses up to 12 mg/kg/day (36 mg/m<sup>2</sup>/day) and rats at doses up to 9 mg/kg/day (54 mg/m<sup>2</sup>/day), the approximate equivalent of 0.2 times the maximum recommended therapeutic dose of 185 mg/m<sup>2</sup>/day, showed no teratogenic or embryotoxic effects. In separate studies in rabbits, maternally toxic doses were associated with embryotoxicity but not teratogenicity. However, animal reproduction studies are not always predictive of human response. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as ketoprofen, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All

pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

## ***Clinical Considerations***

### *Fetal/Neonatal Adverse Reactions*

#### **Premature Closure of Fetal Ductus Arteriosus**

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including ketoprofen extended-release capsules, can cause premature closure of the fetal ductus arteriosus (see WARNINGS: Fetal Toxicity).

#### *Oligohydramnios/Neonatal Renal Impairment*

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If ketoprofen extended-release capsules treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue ketoprofen extended-release capsules and follow up according to clinical practice (see WARNINGS: Fetal Toxicity).

## ***Data***

### *Human Data*

#### **Premature Closure of Fetal Ductus Arteriosus**

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

#### **Oligohydramnios/Neonatal Renal Impairment**

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term

infant exposed to NSAIDs through maternal use is uncertain.

## **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/m<sup>2</sup>/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**

It is not known whether this drug is excreted in human milk. Data on secretion in human milk after ingestion of ketoprofen do not exist. In rats, ketoprofen at doses of 9 mg/kg (54 mg/m<sup>2</sup>/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**

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

## **Geriatric Use**

As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older). In pharmacokinetic studies, ketoprofen clearance was reduced in older patients receiving ketoprofen extended-release capsules, compared with younger patients. Peak ketoprofen concentrations and free drug AUC were increased in older patients (see PHARMACOKINETICS: Special Populations). The glucuronide conjugate of ketoprofen, which can serve as a potential reservoir for the parent drug, is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. It is recommended that the initial dosage of ketoprofen extended-release capsules should be reduced for patients over 75 years of age and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION). In addition, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients may be more sensitive to the antiprostaglandin effects of NSAIDs (on the gastrointestinal tract and kidneys) than younger patients (see WARNINGS and PRECAUTIONS). In particular, elderly or debilitated patients who receive NSAID therapy seem to tolerate gastrointestinal ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Therefore, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose (see DOSAGE AND ADMINISTRATION).

In ketoprofen capsules clinical studies involving a total of 1540 osteoarthritis or rheumatoid arthritis patients, 369 (24%) were  $\geq$  65 years of age, and 92 (6%) were  $\geq$  75 years of age. For ketoprofen capsules acute pain studies, 23 (5%) of 484 patients were  $\geq$  60 years of age. In ketoprofen extended-release capsules clinical studies, 356

(42%) of 840 osteoarthritis or rheumatoid arthritis patients were  $\geq 65$  years of age, and less than 100 of these were  $\geq 75$  years of age. No overall differences in effectiveness were observed between these patients and younger patients.

## **ADVERSE REACTIONS**

The incidence of common adverse reactions (above 1%) was obtained from a population of 835 ketoprofen capsules-treated patients in double-blind trials lasting from 4 to 54 weeks and in 622 ketoprofen extended-release capsules treated (200 mg/day) patients 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 with 200 mg of ketoprofen extended-release capsules once a day or 75 mg of ketoprofen capsules TID (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 one or more of the following sources: foreign reports to manufacturers and regulatory agencies, publications, U.S. clinical trials, and/or U.S. postmarketing spontaneous reports.

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, hepatic dysfunction, hepatitis, cholestatic hepatitis, jaundice.

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

**Metabolic and Nutritional:** Thirst, weight gain, weight loss, hyponatremia.

**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, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.

**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, 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 g 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 1-2 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) 3-4 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 extended-release ketoprofen 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**

Carefully consider the potential benefits and risks of ketoprofen extended-release capsules and other treatment options before deciding to use ketoprofen extended-release capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

After observing the response to initial therapy with ketoprofen extended-release capsules, the dose and frequency should be adjusted to suit an individual patient's needs.

Concomitant use of ketoprofen extended-release capsules is not recommended.

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 of ketoprofen capsules 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.

In patients with mildly impaired renal function, the maximum recommended total daily dose of ketoprofen extended-release capsules is 150 mg. In patients with a more severe renal impairment (GFR less than 25 mL/min/1.73 m<sup>2</sup> or end-stage renal impairment), the maximum total daily dose of ketoprofen extended-release capsules should not exceed 100 mg.

In elderly patients, renal function may be reduced with apparently normal serum creatinine and/or BUN levels. Therefore, it is recommended that the initial dosage of ketoprofen extended-release capsules should be reduced for patients over 75 years of

age (see PRECAUTIONS: Geriatric Use).

It is recommended that for patients with impaired liver function and serum albumin concentration less than 3.5 g/dL, the maximum initial total daily dose of ketoprofen extended-release capsules should be 100 mg. 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 ketoprofen extended-release capsules and closely monitored.

### **Rheumatoid Arthritis and Osteoarthritis**

The recommended starting dose of ketoprofen in otherwise healthy patients is for ketoprofen extended-release capsules 200 mg administered once a day. Smaller doses of ketoprofen extended-release capsules should be utilized initially in small individuals, or in debilitated or elderly patients. The recommended maximum daily dose of ketoprofen is 200 mg/day for ketoprofen extended-release capsules.

Dosages higher than 200 mg/day of ketoprofen extended-release capsules are not recommended because they have not been studied. Concomitant use of ketoprofen extended-release capsules is not recommended. Relatively smaller people may need smaller doses.

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 extended-release capsules be taken with antacids, food, or milk. Although food delays the absorption of both formulations (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 extended-release capsules in relation to food and/or what patients should do if they experience minor GI symptoms associated with either formulation.

### **Management of Pain and Dysmenorrhea**

Ketoprofen extended-release capsules are not recommended for use in treating acute pain because of its extended-release characteristics.

### **HOW SUPPLIED**

Ketoprofen Extended-Release Capsules, USP are available containing 200 mg of ketoprofen, USP.

The 200 mg capsules are hard-shell gelatin capsules with a blue green opaque cap and an iron gray opaque body filled with white to off-white beads. The capsules are axially printed with **MYLAN** over **8200** in black ink on both the cap and body. They are available as follows:

NDC 0378-8200-01  
bottles of 100 capsules

**Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

**Protect from direct light and excessive heat and humidity.**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

**PHARMACIST:** Dispense a Medication Guide with each prescription.

## **Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

**What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?**

**NSAIDs can cause serious side effects, including:**

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - o with increasing doses of NSAIDs
  - o with longer use of NSAIDs

**Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG).”**

**Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.**

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - o anytime during use
  - o without warning symptoms
  - o that may cause death

**The risk of getting an ulcer or bleeding increases with:**

- o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- o taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs”, or “SNRIs”
  
- o increasing doses of NSAIDs
- o longer use of NSAIDs
- o smoking
- o drinking alcohol
- o older age
- o poor health
- o advanced liver disease
- o bleeding problems

**NSAIDs should only be used:**

- o exactly as prescribed



- o at the lowest dose possible for your treatment
- o for the shortest time needed

### **What are NSAIDs?**

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

### **Who should not take NSAIDs?**

#### **Do not take NSAIDs:**

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

### **Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:**

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

**Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements.** NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

### **What are the possible side effects of NSAIDs?**

**NSAIDs can cause serious side effects, including:**

**See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?”**

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

### **Get emergency help right away if you get any of the following symptoms:**

- shortness of breath or trouble
- slurred speech

- breathing
- chest pain
- weakness in one part or side of your body

- swelling of the face or throat

**Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:**

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

**If you take too much of your NSAID, call your healthcare provider or get medical help right away.**

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

#### **Other information about NSAIDs**

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

#### **General information about the safe and effective use of NSAIDs**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which they were not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. They may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

**Manufactured by:** Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A.  
For more information, call Mylan at 1-877-446-3679 (1-877-4-INFO-RX).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

**Mylan Pharmaceuticals Inc.**  
Morgantown, WV 26505 U.S.A.

Revised: 3/2021

KETO:R15m/MG:KETO:R4m

**PRINCIPAL DISPLAY PANEL - 200 mg**

**NDC 0378-8200-01**

**Ketoprofen  
Extended-Release  
Capsules, USP  
200 mg**

**PHARMACIST: Dispense the accompanying  
Medication Guide to each patient.**

**Rx only      100 Capsules**

Each capsule contains:  
Ketoprofen, USP              200 mg

**Usual Dosage:** See accompanying  
prescribing information.

**Keep this and all medication out of the  
reach of children.**

**Store at 20° to 25°C (68° to 77°F). [See  
USP Controlled Room Temperature.]**

**Protect from direct light and excessive  
heat and humidity.**

Manufactured for:  
**Mylan Pharmaceuticals Inc.**  
Morgantown, WV 26505 U.S.A.

Made in India

**Mylan.com**

**RMX8200A**

Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.

Keep container tightly closed.

Code No.: MH/DRUGS/25/NKD/89

Each capsule contains:  
Ketoprofen, USP 200 mg  
Usual Dosage: See accompanying  
prescribing information.  
Keep this and all medication out of the  
reach of children.  
Store at 20° to 25°C (68° to 77°F). [See  
USP Controlled Room Temperature.]  
Protect from direct light and excessive  
heat and humidity.

Manufactured for:  
Mylan Pharmaceuticals Inc.  
Morgantown, WV 26505 U.S.A.  
Made in India

 [Mylan.com](http://Mylan.com)

RMX8200A

NDC 0378-8200-01

**Ketoprofen**  
**Extended-Release**  
**Capsules, USP**

**200 mg**



PHARMACIST: Dispense the accompanying  
Medication Guide to each patient.

 **Mylan**<sup>®</sup>

Rx only

100 Capsules



Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.  
Keep container tightly closed.  
Code No.: MH/DRUGS/25/NKD/89

75074667

(40 x 15 mm)  
Varnish Free area for  
Variable Data Coding

## KETOPROFEN

ketoprofen capsule, extended release

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:0378-8200
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>KETOPROFEN</b> (UNII: 90Y4QC304K) (KETOPROFEN - UNII:90Y4QC304K)	KETOPROFEN	200 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>AMMONIA</b> (UNII: 5138Q19F1X)	
<b>FERROSFERRIC OXIDE</b> (UNII: XM0M87F357)	
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>DIBUTYL SEBACATE</b> (UNII: 4W5IH7FLNY)	
<b>ETHYLCELLULOSE, UNSPECIFIED</b> (UNII: 7Z8S9VYZ4B)	
<b>FD&amp;C BLUE NO. 2</b> (UNII: L06K8R7DQK)	
<b>GELATIN, UNSPECIFIED</b> (UNII: 2G86QN327L)	
<b>HYPROMELLOSE, UNSPECIFIED</b> (UNII: 3NXW29V3WO)	
<b>MALTODEXTRIN</b> (UNII: 7CVR7L4A2D)	
<b>METHACRYLIC ACID - METHYL METHACRYLATE COPOLYMER (1:2)</b> (UNII: 5KY68S2577)	
<b>OLEIC ACID</b> (UNII: 2UMI9U37CP)	
<b>SODIUM LAURYL SULFATE</b> (UNII: 368GB5141J)	
<b>SUCROSE</b> (UNII: C151H8M554)	
<b>STARCH, CORN</b> (UNII: O8232NY3SJ)	
<b>TALC</b> (UNII: 7SEV7J4R1U)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	
<b>TRIACETIN</b> (UNII: XHX3C3X673)	
<b>TRIETHYL CITRATE</b> (UNII: 8Z96QXD6UM)	

<b>FERRIC OXIDE YELLOW</b> (UNII: EX438O2MRT)	
<b>D&amp;C YELLOW NO. 10</b> (UNII: 35SW5USQ3G)	
<b>FD&amp;C BLUE NO. 1</b> (UNII: H3R47K3TBD)	
<b>FD&amp;C RED NO. 40</b> (UNII: WZB9127XOA)	
<b>PROPYLENE GLYCOL</b> (UNII: 6DC9Q167V3)	
<b>SHELLAC</b> (UNII: 46N107B71O)	

### Product Characteristics

<b>Color</b>	BLUE (blue green opaque) , GRAY (iron gray opaque)	<b>Score</b>	no score
<b>Shape</b>	CAPSULE	<b>Size</b>	22mm
<b>Flavor</b>		<b>Imprint Code</b>	MYLAN;8200
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-8200-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/04/2003	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075679	09/04/2003	

**Labeler** - Mylan Pharmaceuticals Inc. (059295980)

Revised: 3/2021

Mylan Pharmaceuticals Inc.