FELDENE®
(piroxicam)
CAPSULES
10 mg and 20 mg
For Oral Use

Cardiovascular Risk

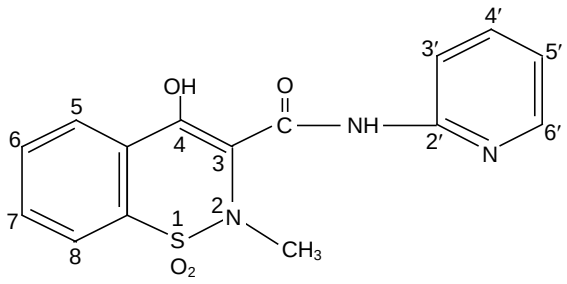
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**).
- FELDENE® is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **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 events (see **WARNINGS).**

DESCRIPTION

FELDENE® contains piroxicam which is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each maroon and blue capsule contains 10 mg piroxicam, each maroon capsule contains 20 mg piroxicam for oral administration. The chemical name for piroxicam is 4-hydroxyl-2-methyl-*N*-2-pyridinyl-2*H*-1,2,-benzothiazine-3-carboxamide 1,1-dioxide. Piroxicam occurs as a white crystalline solid, sparingly soluble in water, dilute acid, and most organic solvents. It is slightly soluble in alcohol and in aqueous solutions. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8). The molecular weight of piroxicam is 331.35. Its molecular formula is $C_{15}H_{13}N_3O_4S$ and it has the following structural formula:



The inactive ingredients in FELDENE capsules include: Blue 1, Red 3, lactose, magnesium stearate, sodium lauryl sulfate, starch.

CLINICAL PHARMACOLOGY

Pharmacodynamics

FELDENE is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of FELDENE, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics

Absorption: FELDENE is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses and generally peak within three to five hours after medication. The prolonged half-life (50 hours) results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/mL, while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg FELDENE, usually stabilize at 3–8 mcg/mL. Most patients approximate steady state plasma levels within 7–12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

With food there is a slight delay in the rate but not the extent of absorption following oral administration. The concomitant administration of antacids (aluminum hydroxide or aluminum hydroxide with magnesium hydroxide) have been shown to have no effect on the plasma levels of orally administered piroxicam.

Distribution: The apparent volume of distribution of piroxicam is approximately 0.14 L/kg. Ninety-nine percent of plasma piroxicam is bound to plasma proteins. Piroxicam is excreted into human milk. The presence in breast milk has been determined during initial and long-term conditions (52 days). Piroxicam appeared in breast milk at about 1% to 3% of the maternal concentration. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment.

Metabolism: Metabolism of piroxicam occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. In vitro studies indicate cytochrome P4502C9 (CYP2C9) as the main enzyme involved in the formation to the 5′-hydroxy-piroxicam, the major metabolite (see ***Pharmacogenetics***, and **Special Populations**, ***Poor Metabolizers of CYP2C9 Substrates***). The biotransformation products of piroxicam metabolism are reported to not have any anti-inflammatory activity.

Higher systemic exposure of piroxicam has been noted in subjects with CYP2C9 polymorphisms compared to normal metabolizer type subjects (see ***Pharmacogenetics***, and **Special Populations**, ***Poor Metabolizers of CYP2C9 Substrates***).

Excretion: FELDENE and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as in the feces. Approximately 5% of a FELDENE dose is excreted unchanged. The plasma half-life ($T_{½}$) for piroxicam is approximately 50 hours.

Pharmacogenetics*:* CYP2C9 activity is reduced in individuals with genetic polymorphisms, such as the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from two published reports showed that subjects with heterozygous CYP2C9*1/*2 (n=9), heterozygous CYP2C9*1/*3 (n=9), and homozygous CYP2C9*3/*3 (n=1) genotypes showed 1.7-, 1.7-, and 5.3-fold higher piroxicam systemic levels, respectively, than the subjects with CYP2C9*1/*1 (n=17, normal metabolizer genotype) following administration of an oral single dose. The mean elimination half life values of piroxicam for subjects with CYP2C9*1/*3 (n=9) and CYP2C9*3/*3 (n=1) genotypes were 1.7- and 8.8-fold higher than subjects with CYP2C9*1/*1 (n=17). It is estimated that the frequency of the homozygous*3/*3 genotype is 0% to 1% in the population at large; however, frequencies as high as 5.7% have been reported in certain ethnic groups.

Special Populations

Pediatric: FELDENE has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency: The effects of hepatic disease on FELDENE pharmacokinetics have not been established. However, a substantial portion of FELDENE elimination occurs by hepatic metabolism. Consequently, patients with hepatic disease may require reduced doses of FELDENE as compared to patients with normal hepatic function.

Poor Metabolizers of CYP2C9 Substrates: Patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin and phenytoin) should be administered piroxicam with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Renal Insufficiency: FELDENE pharmacokinetics have been investigated in patients with renal insufficiency. Studies indicate patients with mild to moderate renal impairment may not require dosing adjustments. However, the pharmacokinetic properties of FELDENE in patients with severe renal insufficiency or those receiving hemodialysis are not known.

Other Information

In controlled clinical trials, the effectiveness of FELDENE has been established for both acute exacerbations and long-term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of FELDENE are evident early in the treatment of both diseases with a progressive increase in response over several (8–12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation.

Doses of 20 mg/day FELDENE display a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

FELDENE has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a “steroid-sparing” effect has not been adequately studied to date.

INDICATIONS AND USAGE

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

FELDENE is indicated:

- For relief of the signs and symptoms of osteoarthritis.
- For relief of the signs and symptoms of rheumatoid arthritis.

CONTRAINDICATIONS

FELDENE is contraindicated in patients with known hypersensitivity to piroxicam.

FELDENE 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-like reactions to NSAIDs have been reported in such patients (see **WARNINGS: Anaphylactoid Reactions** and **PRECAUTIONS: Preexisting Asthma**).

FELDENE is contraindicated for the treatment of peri-operative pain 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, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or 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 does increase the risk of serious GI events (see **WARNINGS, Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation**).

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 (see **CONTRAINDICATIONS**).

Hypertension
NSAIDs, including FELDENE, can lead to onset of new hypertension or worsening of preexisting 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 FELDENE, 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.

Congestive Heart Failure and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs. FELDENE should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation
NSAIDs, including FELDENE, 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 3–6 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 of 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 ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI 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 greatest 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 FELDENE in patients with advanced renal disease. Therefore, treatment with FELDENE is not recommended in these patients with advanced renal disease. If FELDENE 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 FELDENE. FELDENE 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: Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
NSAIDs, including FELDENE, 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.

Other Hypersensitivity Reactions
A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculobullous reactions and exfoliative dermatitis.

Pregnancy
In late pregnancy, as with other NSAIDs, FELDENE should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General
FELDENE 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.

The pharmacological activity of FELDENE in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including FELDENE. 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 more severe hepatic reaction while on therapy with FELDENE. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued (see **ADVERSE REACTIONS**).

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including FELDENE. 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 FELDENE, 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 FELDENE who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Ophthalmologic Effects
Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluations.

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, FELDENE should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Reversible Delayed Ovulation
Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including FELDENE, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women taking NSAIDs have also shown a reversible delay in ovulation. Therefore, in women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including FELDENE, should be considered.

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.

- FELDENE, like other NSAIDs, may cause CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, CARDIOVASCULAR EFFECTS**).

- FELDENE, 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 signs 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**).

- FELDENE, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

- Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

- 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.

- 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**).

- In late pregnancy, as with other NSAIDs, FELDENE should be avoided because it may cause premature closure of the ductus arteriosus.

- Advise females of reproductive potential who desire pregnancy that NSAIDs, including Feldene, may be associated with a reversible delay in ovulation For women who have difficulties conceiving, or who are undergoing investigation of infertility, use of piroxicam is not recommended (see **PRECAUTIONS--Reversible Delayed Ovulation**).

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs and 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, FELDENE should be discontinued.

Drug Interactions

Highly Protein Bound Drugs: FELDENE is highly protein bound and, therefore, might be expected to displace other protein bound drugs. Physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on other highly protein bound drugs.

Aspirin: When FELDENE is administered with aspirin, its protein binding is reduced, although the clearance of free FELDENE is not altered. Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered (20 mg/day) in conjunction with aspirin (3900 mg/day). The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of piroxicam and aspirin is not generally recommended because of the potential for increased adverse effects.

Methotrexate: 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.

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.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

Diuretics: Clinical studies, as well as postmarketing observations, have shown that FELDENE can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. 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.

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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Piroxicam has not been adequately evaluated for carcinogenicity.

Piroxicam was not mutagenic in an Ames bacterial reverse mutation assay, or in a dominant lethal mutation assay in mice, and was not clastogenic in an in vivo chromosome aberration assay in mice.

Reproductive studies in which rats were administered piroxicam at doses of 2, 5, or 10 mg/kg/day (up to 5 times the maximum recommended human dose [MRHD] of 20 mg based on mg/m^2 body surface area [BSA]) revealed no impairment of male or female fertility.

Pregnancy
Pregnancy Category C First and Second Trimester
Pregnancy Category D Third Trimester

There are no adequate and well-controlled studies of FELDENE (piroxicam) in pregnant women. Use of NSAIDs, including FELDENE, during the third trimester of pregnancy increases the risk of premature closure of the ductus arteriosus. All pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. During the first and second trimesters of pregnancy, use FELDENE only if the potential benefit justifies the potential risk to the fetus. During the third trimester of pregnancy, the patient should be apprised of the potential hazard to a fetus.

Pregnant rats administered piroxicam 2, 5, or 10 mg/kg/day during the period of organogenesis (gestation days 6 to 15) demonstrated increased post-implantation losses with 5 and 10 mg/kg/day of piroxicam (equivalent to 3 and 5 times the maximum recommended human dose [MRHD], of 20 mg respectively, based on a mg/m^2 body surface area [BSA]). There were no drug-related developmental abnormalities noted in offspring. Gastrointestinal tract toxicity was increased in pregnant rats in the last trimester of pregnancy compared to non-pregnant rats or rats in earlier trimesters of pregnancy. Pregnant rabbits administered piroxicam 2, 5, or 10 mg/kg/day during the period of organogenesis (gestation days 7 to 18) demonstrated no drug-related developmental abnormalities in offspring (up to 11 times the MRHD based on a mg/m^2 BSA).

Based on animal data, prostaglandins have shown an important role in endometrial vascular permeability, blastocyst implantation and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as piroxicam, have been shown to result in increased pre- and post-implantation loss.

In a pre- and post-natal development study in which pregnant rats were administered piroxicam 2, 5, or 10 mg/kg/day on gestation day 15 through delivery and weaning of offspring, reduced weight gain and death were observed in dams at 10 mg/kg/day starting gestation day 20 (5 times the MRHD based on a mg/m^2 BSA). Treated dams revealed peritonitis, adhesions, gastric bleeding, hemorrhagic enteritis and dead fetuses in utero. Parturition was delayed in all piroxicam-treated groups, and there was an increased incidence of stillbirth. Postnatal development could not be reliably assessed due to the absence of maternal care secondary to severe maternal toxicity.

Labor and Delivery
The effects of FELDENE on labor or delivery in pregnant women are unknown. In rat studies with piroxicam, as with other drugs known to inhibit prostaglandin synthesis, delayed parturition and an increased incidence of stillbirth were noted at doses equivalent to the MRHD of piroxicam.

Nursing Mothers
Piroxicam is present in human milk at about 1% to 3% of the maternal concentration. No accumulation of piroxicam occurred in milk relative to that in maternal plasma during treatment. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for

FELDENE and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Exercise caution when FELDENE is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
As with any NSAID, caution should be exercised in treating the elderly (65 years and older). Most spontaneous reports of fatal GI events with NSAIDs are in the elderly or debilitated patients and, therefore, care should be taken in treating this population. In addition to a past history of ulcer disease, older age and poor general health status (among other factors) may increase the risk for GI bleeding. To minimize the potential risk of an adverse GI event, the lowest effective dose should be used for the shortest possible duration (see **WARNINGS, Gastrointestinal Effects – Risk of Ulceration, Bleeding, and Perforation**).

As with all other NSAIDs, there is a risk of developing renal toxicity in patients in which renal prostaglandins have a compensatory role in maintenance of renal perfusion. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state (see **Warnings: Renal Effects**).

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting a greater frequency of impaired drug elimination and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

In patients taking FELDENE or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1–10% of patients are:

Cardiovascular System: Edema.

Digestive System: Anorexia, abdominal pain, constipation, diarrhea, dyspepsia, elevated liver enzymes, flatulence, gross bleeding/perforation, heartburn, nausea, ulcers (gastric/duodenal), vomiting.

Hemic and Lymphatic System: Anemia, increased bleeding time.

Nervous System: Dizziness, headache.

Skin and Appendages: Pruritus, rash.

Special Senses: Tinnitus.

Urogenital System: Abnormal renal function.

Additional adverse experiences reported occasionally include:

Body As a Whole: Fever, infection, sepsis.

Cardiovascular System: Congestive heart failure, hypertension, tachycardia, syncope.

Digestive System: Dry mouth, esophagitis, gastritis, glossitis, hematemesis, hepatitis, jaundice, melena, rectal bleeding, stomatitis.

Hemic and Lymphatic System: Ecchymosis, eosinophilia, epistaxis, leukopenia, purpura, petechial rash, thrombocytopenia.

Metabolic and Nutritional: Weight changes, fluid retention.

Nervous System: Anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo.

Respiratory System: Asthma, dyspnea.

Skin and Appendages: Alopecia, bruising, desquamation, erythema, photosensitivity, sweat.

Special Senses: Blurred vision.

Urogenital System: Cystitis, dysuria, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, oliguria/polyuria, proteinuria, renal failure, glomerulonephritis.

Other adverse reactions which occur rarely are:

Body As a Whole: Anaphylactic reactions, appetite changes, death, flu-like syndrome, pain (colic), serum sickness.

Cardiovascular System: Arrhythmia, exacerbation of angina, hypotension, myocardial infarction, palpitations, vasculitis.

Digestive System: Eructation, liver failure, pancreatitis.

Hemic and Lymphatic System: Agranulocytosis, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia.

Hypersensitivity: Positive ANA.

Metabolic and Nutritional: Hyperglycemia, hypoglycemia.

Nervous System: Akathisia, convulsions, coma, hallucinations, meningitis, mood alterations.

Respiratory: Respiratory depression, pneumonia.

Skin and Appendages: Angioedema, toxic epidermal necrosis, erythema multiforme, exfoliative dermatitis, onycholysis, Stevens-Johnson Syndrome, urticaria, vesiculobullous reaction.

Special Senses: Conjunctivitis, hearing impairment, swollen eyes.

Reproductive system and breast disorders: Female fertility decreased.

OVERDOSAGE

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60–100 g in adults, 1–2 g/kg in children) and/or osmotic cathartic may be indicated. The long plasma half-life of piroxicam should be considered when treating an overdose with piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam by more than 50% and systemic bioavailability by as much as 37% when activated charcoal is given as late as 6 hours after ingestion of piroxicam. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of FELDENE and other treatment options before deciding to use FELDENE. 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 FELDENE, the dose and frequency should be adjusted to suit an individual patient's needs.

For the relief of rheumatoid arthritis and osteoarthritis, the recommended dose is 20 mg given orally once per day. If desired, the daily dose may be divided. Because of the long half-life of FELDENE, steady-state blood levels are not reached for 7–12 days. Therefore, although the therapeutic effects of FELDENE are evident early in treatment, there is a progressive increase in response over several weeks and the effect of therapy should not be assessed for two weeks.

HOW SUPPLIED

FELDENE® Capsules for oral administration:

Bottles of 100: 10 mg (NDC 0069-3220-66) maroon and blue #322

Bottles of 100: 20 mg (NDC 0069-3230-66) maroon #323

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.
This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?
NSAID medicines 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 a Non-Steroidal Anti-Inflammatory Drug (NSAID)?
Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

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

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

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

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine 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 of these NSAID medicines 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.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

* Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

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

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