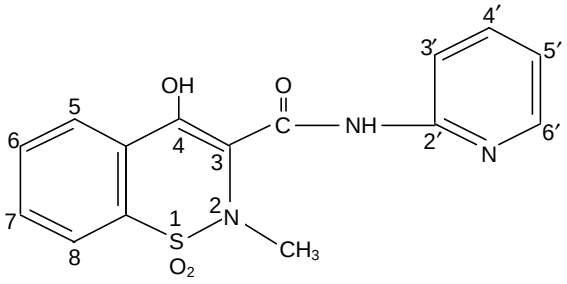
65-4100-00-6.1

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

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. The biotransformation products of piroxicam metabolism are reported to not have any anti-inflammatory activity.

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.

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.

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

FELDENE is indicated for acute or long-term use in the relief of signs and symptoms of the following:

1. Osteoarthritis.
2. 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**).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation
Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused

by NSAIDs, appear to 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 thus, 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. 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, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with *a prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other cotherapies or comorbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

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.

Advanced Renal Disease
In cases with advanced kidney disease, treatment with FELDENE is not recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see **PRECAUTIONS: Renal Effects**).

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**).

Renal Effects
Caution should be used when initiating treatment with FELDENE in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with FELDENE. Caution is also recommended in patients with preexisting kidney disease (see **WARNINGS: Advanced Renal Disease**).

As with other NSAIDs, long-term administration of FELDENE has resulted in renal papillary necrosis and other renal medullary changes. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria and occasionally, nephrotic syndrome. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of 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 nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Because of extensive renal excretion of piroxicam and its biotransformation products less than 5% of the daily dose is excreted unchanged (see **CLINICAL PHARMACOLOGY**), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including FELDENE. This may be due to fluid retention, 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.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

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. FELDENE does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). 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.

Fluid Retention and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore, as with other NSAIDs, FELDENE should be used with caution in patients with fluid retention, hypertension, or heart failure.

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.

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.

Information for Patients
FELDENE, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulceration and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulceration and bleeding, and should ask for medical advice when observing any indicative sign or symptom. Patients should be apprised of the

importance of this follow-up (see **WARNINGS: Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation**).

Patients should report to their physicians, signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

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 also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see **WARNINGS**).

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

Laboratory Tests
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: 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). 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.

Furosemide: Clinical studies, as well as post-marketing 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 **PRECAUTIONS: 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
Subacute, acute and chronic toxicity studies have been carried out in rats, mice, dogs and monkeys. The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see **PRECAUTIONS**) and gastrointestinal lesions.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy
Teratogenic Effects: Pregnancy Category C – Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. FELDENE is not recommended for use in pregnant women since safety has not been established in humans.

Nonteratogenic Effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. In animal studies, gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to nonpregnant females or females in earlier trimesters of pregnancy.

Labor and Delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of FELDENE on labor and delivery in pregnant women are unknown.

Nursing Mothers
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. FELDENE is not recommended for use in nursing mothers.

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. 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 (GI) Effects – Risk of GI 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 **PRECAUTIONS: 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. However, whether controlled clinical studies of FELDENE included sufficient numbers of subjects aged 65 and over to define a difference in response from younger subjects has not been determined.

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.

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.

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.

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

As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, 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
20 mg (NDC 0069-3230-66) maroon #323

Bottles of 500: 20 mg (NDC 0069-3230-73) maroon #323

Rx only

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