

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Caldolor safely and effectively. See full prescribing information for Caldolor.

CALDOLOR (ibuprofen) Injection, for intravenous use
Initial U.S. Approval: 1974

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning

Cardiovascular Risk

- Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use. (5.1)
- Caldolor is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. (4.3, 5.1)

Gastrointestinal Risk

- NSAIDs increase the risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Events can occur at any time without warning symptoms. Elderly patients are at greater risk. (5.2)

INDICATIONS AND USAGE

Caldolor is an NSAID indicated in adults for the:

- Management of mild to moderate pain (1.1)
- Management of moderate to severe pain as an adjunct to opioid analgesics (1.1)
- Reduction of fever (1.2)

DOSAGE AND ADMINISTRATION

- Pain: 400 mg to 800 mg intravenously over 30 minutes every 6 hours as necessary. (2.1)
- Fever: 400 mg intravenously over 30 minutes, followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary. (2.2)
- Patients must be well hydrated before Caldolor administration.
- Caldolor must be diluted before administration. (2.3)

DOSAGE FORMS AND STRENGTHS

Vials: 400 mg/4 mL or 800 mg/8 mL (3)

CONTRAINDICATIONS

- Known hypersensitivity to ibuprofen or other NSAIDs (4.1)
- Asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs (4.2)
- Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery (4.3, 5.1)

WARNINGS AND PRECAUTIONS

- Serious and potentially fatal CV thrombotic events: Use lowest effective dose of Caldolor for shortest possible duration. (5.1)

- Serious and potentially fatal GI reactions: Use lowest effective dose of Caldolor for shortest possible duration. Use with caution in patients with prior history of ulcer disease or GI bleeding. (5.2)
- Hepatic effects: Range from transaminase elevations to liver failure. Discontinue Caldolor immediately if abnormal liver tests persist or worsen. (5.3, 5.15)
- Hypertension: Can occur with NSAID treatment. Monitor blood pressure closely during treatment with Caldolor. (5.4)
- Congestive heart failure and edema: Fluid retention and edema can occur with NSAID treatment. Use Caldolor with caution in patients with fluid retention or heart failure. (5.5)
- Renal effects: Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury. Use Caldolor with caution in patients at risk (e.g., the elderly, those with renal impairment, heart failure, liver impairment, and those taking diuretics or ACE inhibitors). (5.6)
- Anaphylactoid reactions: May occur in patients with the aspirin triad or in patients without prior exposure to Caldolor. Discontinue Caldolor immediately if an anaphylactoid reaction occurs. (5.7, 5.12)
- Serious skin reactions: Include exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal. Discontinue Caldolor if rash or other signs of local skin reaction occur. (5.8)

ADVERSE REACTIONS

The most common adverse reactions are nausea, flatulence, vomiting, headache, hemorrhage and dizziness (>5%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cumberland Pharmaceuticals Inc. at 1-877-484-2700 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- ACE-inhibitors: NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. (7.3)
- Aspirin: Concomitant administration of ibuprofen and aspirin is not generally recommended because of the potential for increased adverse effects. (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Avoid use after 30 weeks gestation because premature closure of the ductus arteriosus in the fetus may occur. (8.1)
- Nursing Mothers: Use with caution as it is not known if ibuprofen is excreted in human milk. (8.3)
- Pediatric Use: Safety and effectiveness not established in patients less than 17 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Risk

- Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of serious cardiovascular (CV) 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 and Precautions (5.1)*].
- Caldolor is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Contraindications (4.3) and Warnings and Precautions (5.1)*].

Gastrointestinal Risk

- NSAIDs increase the risk of serious gastrointestinal (GI) 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 and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 Analgesia (Pain)

Caldolor is indicated in adults for the management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics.

1.2 Antipyretic (Fever)

Caldolor is indicated for the reduction of fever in adults.

2 DOSAGE AND ADMINISTRATION

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*]. After observing the response to initial therapy with Caldolor, the dose and frequency should be adjusted to suit an individual patient's needs. Do not exceed 3200 mg total daily dose.

To reduce the risk of renal adverse reactions, patients must be well hydrated prior to administration of Caldolor.

2.1 Analgesia (Pain)

Administer 400 mg to 800 mg intravenously every 6 hours as necessary. Infusion time must be no less than 30 minutes.

2.2 Antipyretic (Fever)

Administer 400 mg intravenously, followed by 400 mg every 4 to 6 hours or 100-200 mg every 4 hours as necessary. Infusion time must be no less than 30 minutes.

2.3 Preparation and Administration

Caldolor **must be diluted** prior to intravenous infusion. Dilute to a final concentration of 4 mg/mL or less. Appropriate diluents include 0.9% Sodium Chloride Injection USP (normal saline), 5% Dextrose Injection USP (D5W), or Lactated Ringers Solution.

- 800 mg dose: Dilute 8 mL of Caldolor in no less than 200 mL of diluent.
- 400 mg dose: Dilute 4 mL of Caldolor in no less than 100 mL of diluent.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

Diluted solutions are stable for up to 24 hours at ambient temperature (approximately 20 to 25° C) and room lighting.

Infusion time must be no less than 30 minutes.

3 DOSAGE FORMS AND STRENGTHS

Caldolor is available as a 400 mg/4 mL single-dose vial (100 mg/mL) and 800 mg/8 mL single-dose vial (100 mg/mL).

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Caldolor is contraindicated in patients with known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to ibuprofen. [see *Warnings and Precautions (5.7, 5.8)*]

4.2 Asthma and Allergic Reactions

Caldolor is contraindicated in 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 and Precautions (5.7, 5.12)*].

4.3 Coronary Artery Bypass Graft (CABG)

Caldolor is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 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, use the lowest effective dose 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.

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 (4.3)*].

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 gastrointestinal (GI) events [see *Warnings and Precautions (5.2)*].

5.2 Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including ibuprofen, can cause serious 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.

Prescribe NSAIDs, including Caldolor, with extreme caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to treated 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 reports of spontaneous 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, use the lowest effective dose 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.

5.3 Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including ibuprofen. 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 have been reported, including jaundice, fulminant hepatitis, liver necrosis and hepatic failure, some with fatal outcomes. A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ibuprofen. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ibuprofen should be discontinued.

5.4 Hypertension

NSAIDs, including ibuprofen, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including ibuprofen, with caution in patients with hypertension. Monitor blood pressure closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE inhibitors, thiazides, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

5.5 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Use Caldolor with caution in patients with fluid retention or heart failure.

5.6 Renal Effects

Use caution when initiating treatment with Caldolor in patients with considerable dehydration.

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 an NSAID 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 or ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of Caldolor in patients with advanced renal disease. If Caldolor therapy must be initiated in patients with advanced renal disease, closely monitor the patient's renal function.

5.7 Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ibuprofen. CALDOLOR is contraindicated in 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 (4.2)*].

5.8 Serious Skin Reactions

NSAIDs, including ibuprofen, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin manifestations, and to discontinue Caldolor at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy

Starting at 30 weeks gestation, Caldolor, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur [see *Use in Specific Populations (8.1)*].

5.10 Masking Inflammation and Fever

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

5.11 Hematological Effects

Caldolor must be diluted prior to use. Infusion of the drug product without dilution can cause hemolysis [see *Dosage and Administration (2.3)*].

Anemia may occur in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect on erythropoiesis. In patients on long-term treatment with NSAIDs, including ibuprofen, check hemoglobin or hematocrit if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effects on platelet function are less severe quantitatively, of shorter duration, and reversible. Carefully monitor patients who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

5.12 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 between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, including bronchospasm, Caldolor is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

5.13 Ophthalmological Effects

Blurred or diminished vision, scotomata, and changes in color vision have been reported with oral ibuprofen. Discontinue ibuprofen if a patient develops such complaints, and refer the patient for an ophthalmologic examination that includes central visual fields and color vision testing.

5.14 Aseptic Meningitis

Aseptic meningitis with fever and coma has been observed in patients on oral ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, give consideration to whether or not the signs or symptoms are related to ibuprofen therapy.

5.15 Monitoring

Because serious GI tract ulcerations 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 CBC and chemistry profiles checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash), or abnormal liver tests persist or worsen, discontinue Caldolor.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular thrombotic events [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Gastrointestinal effects [see *Boxed Warning and Warnings and Precautions (5.2)*]
- Hepatic effects [see *Warnings and Precautions (5.3)*]
- Hypertension [see *Warnings and Precautions (5.4)*]
- Congestive heart failure and edema [see *Warnings and Precautions (5.5)*]
- Renal effects [see *Warnings and Precautions (5.6)*]
- Anaphylactoid reactions [see *Warnings and Precautions (5.7)*]
- Serious skin reactions [see *Warnings and Precautions (5.8)*]

The most common adverse reactions reported in clinical studies are nausea, flatulence, vomiting, and headache.

The most common reason for discontinuation due to adverse events in controlled trials of Caldolor is pruritus (<1%).

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared directly to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical development, 560 patients were exposed to Caldolor, 438 in pain and 122 with fever. In the pain studies, Caldolor was started intra-operatively and administered at a dose of 400 mg or 800 mg every six hours for up to three days. In the fever studies, Caldolor was administered at doses of 100 mg, 200 mg, or 400 mg every four or six hours for up to 3 days.

The most frequent type of adverse reaction occurring with oral ibuprofen is gastrointestinal.

Pain Studies

The incidence rates of adverse reactions listed in the following table were derived from multicenter, controlled clinical studies in post-operative patients comparing Caldolor to placebo in patients also receiving morphine as needed for post-operative pain.

Table 1: Post-operative Patients with Adverse Reactions Observed in ≥ 3% of Patients in any Caldolor Treatment Group in Pain Studies*

Event	Caldolor		Placebo (N=287)
	400 mg (N=134)	800 mg (N=304)	
<i>Any Reaction</i>	118 (88%)	260 (86%)	258 (90%)
Nausea	77 (57%)	161 (53%)	179 (62%)
Vomiting	30 (22%)	46 (15%)	50 (17%)
Flatulence	10 (7%)	49 (16%)	44 (15%)
Headache	12 (9%)	35 (12%)	31 (11%)
Hemorrhage	13 (10%)	13 (4%)	16 (6%)
Dizziness	8 (6%)	13 (4%)	5 (2%)
Edema peripheral	1 (<1%)	9 (3%)	4 (1%)
Urinary retention	7 (5%)	10 (3%)	10 (3%)
Anemia	5 (4%)	7 (2%)	6 (2%)
Decreased hemoglobin	4 (3%)	6 (2%)	3 (1%)
Dyspepsia	6 (4%) ⁺	4 (1%)	2 (<1%)
Wound hemorrhage	4 (3%)	4 (1%)	4 (1%)
Abdominal discomfort	4 (3%) ⁺	2 (<1%)	0
Cough	4 (3%) ⁺	2 (<1%)	1 (<1%)
Hypokalemia	5 (4%)	3 (<1%)	8 (3%)

* All patients received concomitant morphine during these studies.

Fever Studies

Fever studies were conducted in febrile hospitalized patients with malaria and febrile hospitalized patients with varying causes of fever. In hospitalized febrile patients with malaria, the adverse reactions observed in at least two Caldolor-treated patients included abdominal pain and nasal congestion.

In hospitalized febrile patients (all causes), adverse reactions observed in more than two patients in any given treatment group are presented in the table below.

Table 2: Patients with Adverse Reactions Observed in ≥ 3% of Patients in any Caldolor Treatment Group in All-Cause Fever Study

Event	Caldolor			Placebo (N=28)
	100 mg (N=30)	200 mg (N=30)	400 mg (N=31)	
<i>Any Reaction</i>	27 (87%)	25 (83%)	23 (74%)	25 (89%)
Anemia	5 (17%)	6 (20%)	11 (36%)	4 (14%)
Eosinophilia	7 (23%)	7 (23%)	8 (26%)	7 (25%)
Hypokalemia	4 (13%)	4 (13%)	6 (19%)	5 (18%)
Hypoproteinemia	3 (10%)	0	4 (13%)	2 (7%)
Neutropenia	2 (7%)	2 (7%)	4 (13%)	2 (7%)
Blood urea increased	0	0	3 (10%)	0
Hypernatremia	2 (7%)	0	3 (10%)	0

Table 2: Patients with Adverse Reactions Observed in ≥ 3% of Patients in any Caldolor Treatment Group in All-Cause Fever Study

Event	Caldolor			Placebo N=28
	100 mg N=30	200 mg N=30	400 mg N=31	
Hypertension	0	0	3 (10%)	0
Hypoalbuminemia	3 (10%)	1 (3%)	3 (10%)	1 (4%)
Hypotension	0	2 (7%)	3 (10%)	1 (4%)
Diarrhea	3 (10%)	3 (10%)	2 (7%)	2 (7%)
Pneumonia bacterial	3 (10%)	1 (3%)	2 (7%)	0
Blood LDH increased	3 (10%)	2 (7%)	1 (3%)	1 (4%)
Thrombocytopenia	3 (10%)	2 (7%)	1 (3%)	0
Bacteremia	4 (13%)	0	0	0

7 DRUG INTERACTIONS

7.1 Aspirin

When ibuprofen is administered with aspirin, ibuprofen's protein binding is reduced, although the clearance of free ibuprofen is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of Caldolor and aspirin is not generally recommended because of the potential for increased adverse effects.

7.2 Anticoagulants

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that the users of both drugs together have a higher risk of serious GI bleeding than users of either drug alone [see *Warnings and Precautions* (5.2)].

7.3 ACE Inhibitors

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

7.4 Diuretics

Clinical studies and postmarketing observations have shown that ibuprofen can reduce the natriuretic effects of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, observe patients closely for signs of renal failure, as well as to assure diuretic efficacy [see *Warnings and Precautions* (5.6)].

7.5 Lithium

NSAIDs have produced elevations of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance of lithium decreased by 20%. This effect has been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity.

7.6 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This indicates that NSAIDs may enhance the toxicity of methotrexate. Use caution when NSAIDs are administered concomitantly with methotrexate.

7.7 H₂ Antagonists

In studies of human volunteers, co-administration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects - Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.

Starting at 30 weeks gestation, Caldolor, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Caldolor can cause fetal harm when administered to a pregnant woman starting at 30 weeks gestation.

There are no adequate, well-controlled studies in pregnant women. Prior to 30 weeks gestation, Caldolor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities.

8.2 Labor and Delivery

The effects of Caldolor on labor and delivery in pregnant women are unknown. In rat studies, maternal exposure to NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, increased the incidence of dystocia and delayed parturition, and decreased pup survival.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Caldolor, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Caldolor for management of pain and reduction of fever has not been established in pediatric patients below the age of 17 years.

8.5 Geriatric Use

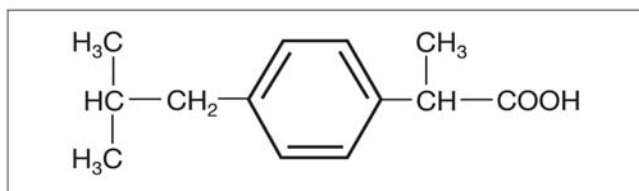
Clinical studies of Caldolor did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients are at increased risk for serious GI adverse events.

10 OVERDOSAGE

The following signs and symptoms have occurred in individuals following an overdose of oral ibuprofen: abdominal pain, nausea, vomiting, drowsiness, and dizziness. There are no specific measures to treat acute overdose with Caldolor. There is no known antidote to ibuprofen. In case of an overdose, discontinue Caldolor therapy and consider contacting a regional poison control center at 1-800-222-1222.

11 DESCRIPTION

Caldolor contains the active ingredient ibuprofen, which is (±)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74-77°C. It has a molecular weight of 206.28. It is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone. The structural formula of ibuprofen is represented below:



Each 1 mL of solution contains 100 mg of ibuprofen in Water for Injection, USP. The product also contains 78 mg/mL arginine at a molar ratio of 0.92:1 arginine:ibuprofen. The solution pH is about 7.4.

Caldolor is sterile and is intended for intravenous administration only.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibuprofen's mechanism of action, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition. Caldolor possesses anti-inflammatory, analgesic, and antipyretic activity.

12.3 Pharmacokinetics

Ibuprofen is a racemic mixture of [-]R- and [+]S-isomers. In vivo and in vitro studies indicate that the [+]S-isomer is responsible for clinical activity. The [-]R-form, while thought to be pharmacologically inactive, is slowly and incompletely (~60%) interconverted into the active [+]S species in adults. The [-]R-isomer serves as a circulating reservoir to maintain levels of active drug. The pharmacokinetic parameters of Caldolor determined in a study with volunteers are presented below.

Table 3: Pharmacokinetic Parameters of Intravenous Ibuprofen		
	400 mg* Caldolor Mean (CV%)	800 mg* Caldolor Mean (CV%)
Number of Patients	12	12
AUC (mcg.h/mL)	109.3 (26.4)	192.8 (18.5)
Cmax (mcg/mL)	39.2 (15.5)	72.6 (13.2)
KEL (1/h)	0.32 (17.9)	0.29 (12.8)
T _{1/2} (h)	2.22 (20.1)	2.44 (12.9)

AUC = Area-under-the-curve
Cmax = Peak plasma concentration
CV = Coefficient of Variation
KEL = First-order elimination rate constant
T_{1/2} = Elimination half-life
* = 30 minute infusion time

Ibuprofen, like most NSAIDs, is highly protein bound (>99% bound at 20 mcg/mL). Protein binding is saturable, and at concentrations >20 mcg/mL binding is nonlinear. Based on oral dosing data, there is an age- or fever-related change in volume of distribution for ibuprofen.

14 CLINICAL STUDIES

14.1 Analgesia (Pain)

The effect of Caldolor on acute pain was evaluated in two multi-center, randomized, double-blind, placebo-controlled studies.

In a study of women who had undergone an elective abdominal hysterectomy, 319 patients were randomized and treated with Caldolor 800 mg or placebo administered every 6 hours (started intra-operatively) and morphine administered on an as needed basis. Efficacy was demonstrated as a statistically significant greater reduction in the mean morphine consumption through 24 hours in patients who received Caldolor as

compared to those receiving placebo (47 mg and 56 mg, respectively). The clinical relevance of this finding is supported by a greater reduction in pain intensity over 24 hours for patients treated with Caldolor, even though morphine was available on an as needed basis

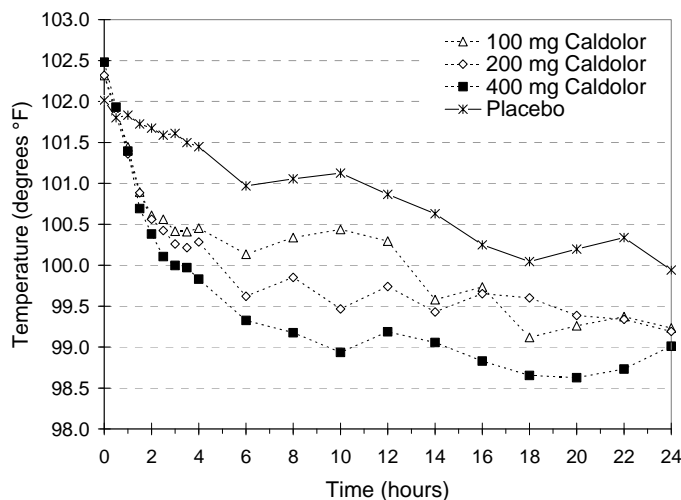
In a study of patients who had undergone an elective abdominal or orthopedic surgery, 406 patients (87 men, 319 women) were randomized to receive Caldolor 400 mg, Caldolor 800 mg, or placebo administered every 6 hours (started intra-operatively), and morphine on an as needed basis. This study failed to demonstrate a statistically significant difference in outcome between patients receiving Caldolor 800 mg or 400 mg and placebo, although there were trends favoring the active treatments.

14.2 Antipyretic (Fever)

The effect of Caldolor on fever was evaluated in two randomized, double-blind studies.

In a multi-center study, 120 hospitalized patients (88 men, 32 women) with temperatures of 101°F or greater were randomized to Caldolor 400 mg, 200 mg, 100 mg or placebo, administered every 4 hours for 24 hours. Each of the three Caldolor doses, 100 mg, 200 mg, and 400 mg, resulted in a statistically greater percentage of patients with a reduced temperature (<101°F) after 4 hours, compared to placebo; (65%, 73%, 77% and 32%, respectively). The dose response is shown in the figure below.

Figure 1: Temperature Reduction by Treatment Group, Hospitalized Febrile Patients



In a single-center study, 60 hospitalized patients (48 men, 12 women) with uncomplicated *P. falciparum* malaria having temperatures $\geq 100.4^\circ\text{F}$ were randomized to Caldolor 400 mg or placebo, administered every 6 hours for 72 hours of treatment. There was a significant reduction in fever within the first 24 hours of treatment, measured as the area above the temperature 98.6°F vs. time curve for patients treated with Caldolor.

16 HOW SUPPLIED/STORAGE AND HANDLING

Caldolor is available in the following strengths:

400 mg/4 mL (100 mg/mL)

Carton of 25 vials, NDC 66220-247-04

800 mg/8 mL (100 mg/mL)

Carton of 25 vials, NDC 66220-287-08

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

The stopper in the Caldolor vial does not contain natural rubber latex, dry natural rubber, or blends of natural rubber.

Manufactured for:
Cumberland Pharmaceuticals Inc.
Nashville, TN 37203
US Patent Number 6,727,286

17 PATIENT COUNSELING INFORMATION

Patients should be informed of the following information before initiating therapy with an NSAID.

17.1 Cardiovascular Effects

Ibuprofen, like other NSAIDs, may cause serious CV events such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, advise patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, and slurring of speech, and to ask for medical advice when observing any indicative sign or symptoms. Inform patients of the importance of this follow-up [see *Warnings and Precautions* (5.1)].

17.2 Gastrointestinal Effects

Ibuprofen, 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, advise patients to be alert for the signs and symptoms of ulcerations and bleeding, and to ask for medical advice when observing any indicative signs or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Inform patients of the importance of this follow-up [see *Warnings and Precautions* (5.2)].

17.3 Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). Instruct patients to stop therapy with Caldolor and seek immediate medical therapy if any of these occur [see *Warnings and Precautions* (5.3)].

17.4 Adverse Skin Reactions

Ibuprofen, 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, advise patients to be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and to ask for medical advice when observing any indicative sign or symptoms. Advise patients to stop Caldolor immediately if they develop any type of rash, and to contact a physician as soon as possible [see *Warnings and Precautions* (5.8)].

17.5 Weight Gain and Edema

Advise patients to promptly report to their physicians signs or symptoms of unexplained weight gain or edema during treatment with Caldolor [see *Warnings and Precautions* (5.5)].

17.6 Anaphylactoid Reactions

Inform patients of the signs of an anaphylactoid reaction (e.g. difficulty in breathing, swelling of the face or throat). If these occur, therapy should be discontinued and medical therapy initiated [see *Warnings and Precautions* (5.7)].

17.7 Effects During Pregnancy

Starting at 30 weeks gestation, Caldolor and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur [see *Use in Specific Populations* (8.1)].