

# CALDOLOR<sup>®</sup>

*(ibuprofen) Injection*

## Product Information Form

American Hospital  
Formulary Service\*

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## Product Information Form for AHFS Drug Information

### 1. AHFS Classification Number

28.08 Analgesics and antipyretics

### 2. Generic Name

ibuprofen

### 3. Source of Supply

Cumberland Pharmaceuticals Inc., Nashville, TN 37203 USA

### 4. New Drug Application (NDA) Number and Date of FDA Approval

NDA 22-348, June 11, 2009

### 5. Physical Properties

#### a. Macroscopic appearance

Caldolor is a clear, colorless solution.

#### b. Solubility

Caldolor is miscible with common diluents, Normal Saline, 5% Dextrose, Lactated Ringers Solution.

### 6. Chemical Properties

#### a. Similarities to other available compounds

NA

#### b. List the pK(s) of the drug

4.4

#### c. Physical or chemical incompatibilities

None known.

#### d. pH range over which Caldolor is stable

Caldolor is stable in unbuffered or mildly buffered diluents such as Normal Saline, 5% Dextrose, and Lactated Ringers Solution.

**e. Recommended storage conditions for Caldolor**

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

**f. Expiration dating periods for commercially available product(s)**

The expiration dating period for Caldolor is 5 years from manufacture.

**g. Excipients contained in the commercially available product(s)**

Each 1 mL of solution contains 100 mg of ibuprofen in Water for Injection, USP. The product also contains 78 mg/mL arginine. The solution pH is approximately 7.4.

**7. Pharmacologic Classification**

**a. Pharmacologic class**

Non-steroidal anti-inflammatory drug (NSAID).

**b. 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.

**c. Pharmacokinetics**

The pharmacokinetic parameters of Caldolor determined in a study with volunteers are presented below.

<b>Pharmacokinetic Parameters of Intravenous Ibuprofen</b>		
	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)
C <sub>max</sub> (mcg/mL)	39.2 (15.5)	72.6 (13.2)
KEL (1/h)	0.32 (17.9)	0.29 (12.8)
T <sub>1/2</sub> (h)	2.22 (20.1)	2.44 (12.9)

AUC = Area-under-the-curve

C<sub>max</sub> = Peak plasma concentration

CV = Coefficient of Variation

KEL = First-order elimination rate constant

T<sub>1/2</sub> = Elimination half-life

\* = 60 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.

## **8. Dosage Range**

### **a. Dosage range and route of administration, by indication**

#### **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. Administer 400 mg to 800 mg intravenously every 6 hours as necessary.

#### **Antipyretic (Fever)**

Caldolor is indicated for the reduction of fever in adults. Administer 400 mg intravenously every 4 to 6 hours or 100-200 mg every 4 hours as necessary.

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. Diluted solutions are stable for seven (7) days at ambient temperature (approximately 20 to 25°C) and room lighting (Data on file, Cumberland Pharmaceuticals Inc.).

- 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.

### **b. Initial, maintenance and maximum doses (dosages) for Caldolor.**

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. 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.

### **c. If modification of the usual dosage recommendations is necessary in geriatric patients, include specific recommendations for this age group.**

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.

### **d. List the pediatric dosage(s) for the drug.**

The current package insert does not contain pediatric dosing.

**e. If specific dosage recommendations exist for renal or hepatic dysfunction, include these.**

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

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.

## 9. Adverse Effects, Toxicities and Special Precautions

**a. Discuss adverse effects of the drug and their frequency of occurrence as determined from research data and human studies; include information from post-marketing surveillance and any important voluntary reports of adverse effects.**

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%).

### Clinical Studies Experience

During clinical development, 560 patients were exposed to Caldolor, 438 with 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.

#### Pain Studies

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

<b>Post-operative Patients with Adverse Reactions Observed in ≥ 3% of Patients in any Caldolor Treatment Group in Pain Studies*</b>			
<b>Event</b>	<b>Caldolor</b>		<b>Placebo (N=287)</b>
	<b>400 mg (N=134)</b>	<b>800 mg (N=304)</b>	
<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%)

<b>Post-operative Patients with Adverse Reactions Observed in ≥ 3% of Patients in any Caldolor Treatment Group in Pain Studies*</b>			
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.

<b>Patients with Adverse Reactions Observed in ≥ 3% of Patients in any Caldolor Treatment Group in All-Cause Fever Study</b>				
<b>Event</b>	<b>Caldolor</b>			<b>Placebo N=28</b>
	<b>100 mg N=30</b>	<b>200 mg N=30</b>	<b>400 mg N=31</b>	
<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
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%)
Thrombocythemia	3 (10%)	2 (7%)	1 (3%)	0
Bacteremia	4 (13%)	0	0	0

**b. Discuss means or methods of prevention or treatment of adverse effects and toxicities. Benefits of disease treatment to risk of adverse effects should be emphasized.**

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. After observing the response to initial therapy with Caldolor, the dose and frequency should be adjusted to suit an individual patient's needs.

**c. List precautions and contraindications for certain disease states or other conditions.**

**CONTRAINDICATIONS**

**Hypersensitivity:** Caldolor is contraindicated in patients with known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to ibuprofen.

**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.

**Coronary Artery Bypass Graft (CABG):** Caldolor is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

**WARNINGS AND PRECAUTIONS**

**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. 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.

**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.

**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.

**Hypertension:** NSAIDs, including ibuprofen, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. 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.

**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.

**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.

**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.

**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.

**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.

**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.

**Hematological Effects:** Caldolor must be diluted prior to use. Infusion of the drug product without dilution can cause hemolysis.

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 values 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.

**Pre-existing 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 pre-existing asthma.

**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.

**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.

**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.

**d. List potential drug-drug interactions if deemed clinically significant.**

**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.

**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.

**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.

**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.

**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.

**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.

**H-2 Antagonists:** In studies of human volunteers, co-administration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

**e. List potential laboratory test interferences if deemed clinically significant.**

Not applicable.

**Before prescribing Caldolor, please read the Prescribing Information available on [www.caldolor.com](http://www.caldolor.com).**

