

PRODUCT INFORMATION

Caldolor®



Caldolor®

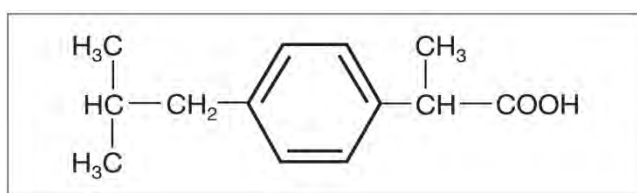
Ibuprofen 400mg in 4mL and 800mg in 8mL concentrated injection

NAME OF THE MEDICINE

Ibuprofen

The molecular weight of the compound is 206.3 and the CAS registry number is 15687-27-1. The molecular formula is $C_{13}H_{18}O_2$

Structural Formula:



DESCRIPTION

Caldolor contains the active ingredient ibuprofen, which is (\pm)-2-(*p*-isobutylphenyl) propionic acid. Ibuprofen is a white powder with a melting point of 74-77°C. It is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone. Ibuprofen has a pKa of 4.43±0.03 and an n-octanol/water partition coefficient of 11.7 at pH 7.4.

Each 1mL of Caldolor injection contains 100 mg of ibuprofen in Water for Injections, USP. Each 1 mL of Caldolor injection also contains 78mg of arginine at a molar ratio of 0.92:1 arginine: ibuprofen. Hydrochloric acid is added for pH adjustment. The solution pH is about 7.4.

Caldolor is sterile and is intended for intravenous administration only.

PHARMACOLOGY

Pharmacodynamics

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.

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.

	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 _{max} (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)
T _{max}	1.05 (15.8)	1.0 (0.0)

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	800 mg Oral Ibuprofen Mean (SD)	800 mg Caldolor Mean (SD)
Number of Patients	12	12
AUC (mcg·h/mL)	196 (36)	196 (37)
C _{max} (mcg/mL)	63 (12)	120 (13)
T _{1/2} (h)	1.9 (0.3)	2.0 (0.5)
T _{max} (h)	1.5	0.11

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

	All Patients Mean(SD)	Critically Ill Mean (SD)	Non-Critically Ill Mean (SD)
AUC (mcg.hr/mL)	70.6 (31.9)	45.9 (16.2)	87.1 (29.2)
C _{max} (mcg/mL)	39.8 (17.8)	25.7 (8.3)	49.1 (16.1)
T _{max} (hr)	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)
T _{1/2} (hr)	2.26 (0.95)	2.32 (0.84)	2.22 (1.05)

AUC = Area-under-the-curve

C_{max} = Peak plasma concentration

CV = Coefficient of Variation

KEL = First-order elimination rate constant

T_{1/2} = Elimination half-life

T_{max} = time of maximum observed plasma concentrations

Ibuprofen, like most NSAIDs, is highly protein bound (>99% bound at 20mcg/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.

CLINICAL TRIALS

Analgesia (Pain)

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

In a study of patients who had undergone an elective orthopaedic surgery, 185 patients (65 men, 120 women) were randomized to receive Caldolor 800 mg or placebo administered every 6 hours (started pre-operatively at study hour 0), and morphine on an as needed basis. Compared to placebo, patients receiving 800 mg intravenous ibuprofen experienced a significant reduction in pain as measured by the VAS-AUC with movement for the post-operative period, study hours 6-28. In the all-treated population, there was a 25.8% reduction in mean area under the visual analogue pain curve (VAS-AUC) (hours 6-28, with movement) in patients receiving intravenous ibuprofen (p<0.001). In addition to experiencing less pain, patients receiving 800 mg intravenous ibuprofen used less morphine. In the all-treated population, there was a 30.9% reduction in mean morphine consumption in patients receiving intravenous ibuprofen for the post-operative period, study hours 6-28 (p<0.001). There were also significant reductions in pain as measured by the VAS-AUC at rest and by the VRS for the post-operative period, study hours 6-28 (p<0.001). In the all-treated population, there was a 31.8% reduction in mean VAS-AUC (at rest) and a 20.2% reduction in mean VRS in patients receiving intravenous ibuprofen (p<0.001). This study did not reveal any increased risk of bleeding events however, the study is not powered sufficiently to confirm the safety of pre-operative commencement of Caldolor.

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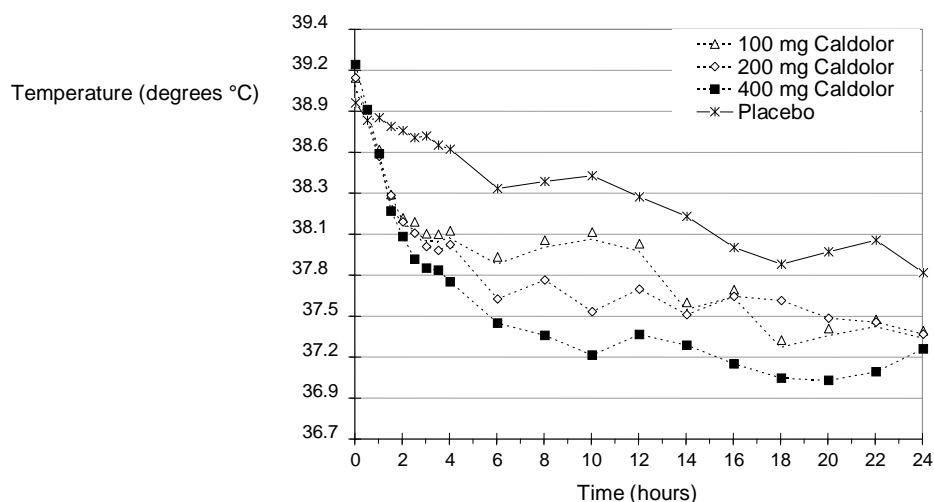
In a study of women who had undergone an elective abdominal hysterectomy, 319 patients were randomized to: Caldolor 800mg, or placebo, administered every 6 hours (started intra-operatively). Both treatment arms were administered with morphine on an as needed basis. Efficacy was demonstrated as a statistically significant greater reduction in the mean morphine consumption through 24 hours in patients who received Caldolor compared to those receiving placebo (47mg and 56mg, 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.

Antipyretic (Fever)

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

In a multi-centre study, 120 hospitalised patients (88 men, 32 women) with temperatures of 38.3°C or greater were randomized to receive either: Caldolor injection 400mg, 200mg, 100mg or placebo, administered every 4 hours for 24 hours. Each of the three Caldolor doses, 100mg, 200mg, and 400mg, resulted in a statistically greater percentage of patients with a reduced temperature (<38.3°C) after 4 hours, compared to placebo (61%, 70%, 77% and 32%, respectively). Comparison with placebo is not significant for the 100mg dose. The dose response is shown in the figure below.

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



In a single-centre study, 60 hospitalised patients (48 men, 12 women) with uncomplicated *P. falciparum* malaria having temperatures $\geq 38.3^\circ\text{C}$ were randomized to receive either Caldolor injection 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 37°C vs. time curve for patients treated with Caldolor.

Study in Hospitalized Adult Patients with Sepsis: A multi-centre study compared a different formulation of I.V. ibuprofen to placebo in 455 patients (282 men, 173 women) who had severe sepsis. Patients were randomized to 10 mg/kg (up to 800 mg) I.V. ibuprofen or placebo, administered every 6 hours for 48 hours of treatment.

INDICATIONS

- Caldolor injection is indicated in adults for the management of acute mild to moderate post-operative pain and moderate to severe post-operative pain with adjunctive reduced morphine dosage, where an intravenous route of administration is considered clinically necessary.
- Caldolor is indicated for the reduction of fever in adults where an intravenous route of administration is considered clinically necessary.

CONTRAINDICATIONS

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

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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 *Precautions*].

Caldolor is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see *Precautions*].

Caldolor is contraindicated in patients with active gastrointestinal bleeding.

Caldolor is contraindicated in patients with spinal cord injuries.

PRECAUTIONS

Duration of Dosage

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 a total daily dose of 3200 mg ibuprofen. Use of the recommended maximum dose of Caldolor 800 mg every 6 hours has only been studied for a period of up to 2 days.

Cardiovascular Thrombotic Events

All NSAIDs have been associated with an increased risk of cardiovascular and thrombotic adverse events when taken long term.

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*].

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.

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 an impaired response to these therapies when taking NSAIDs.

Congestive Heart Failure and Oedema

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

Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation

Serious GI toxicity such as 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 GI 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

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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.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or GI bleeding* and who use NSAIDs, have a greater than 10-fold higher 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 co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, 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.

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.

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 colour 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 colour vision testing.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in some 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 small numbers 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.

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 non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in renal 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, ACE inhibitors, or angiotensin receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

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Caution is also recommended in patients with pre-existing renal disease. 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.

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.

Haematological Effects

Caldolor injection must be diluted prior to use. Infusion of Caldolor injection without dilution can cause haemolysis [see *Dosage and Administration*].

Anaemia 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 haemoglobin or hematocrit if they exhibit any signs or symptoms of anaemia 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.

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 non-infectious, painful conditions.

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*].

Patients Receiving Spinal or Epidural Analgesia

As potential bleeding around the spinal cord has serious consequences, caution should be exercised when treating patients undergoing spinal and epidural analgesia.

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.

Effects on Fertility

In rats, fertility was not affected by dietary administration of ibuprofen 20 mg/kg/day to males and females from prior to mating through organogenesis, or by oral administration to females at up to 180 mg/kg/day throughout gestation. In rabbits, oral administration of ibuprofen 60 mg/kg/day throughout gestation was associated with reduced implantations and live litter size, along with maternotoxicity; the no-effect dose was 20 mg/kg/day.

Use in Pregnancy

Pregnancy Category C

There are no adequate, well-controlled studies in pregnant women. Prior to week 30 of pregnancy, Caldolor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. From week 30 of pregnancy, Caldolor and other NSAIDs can cause fetal harm and should be avoided by pregnant women. NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with NSAIDs during the third trimester of

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pregnancy should only be given on sound indications. During the last few days before expected birth, NSAIDs should be avoided.

There was no evidence of developmental abnormalities following oral administration of ibuprofen to rats and rabbits throughout gestation at respective doses up to 180 and 60 mg/kg/day.

Labour and Delivery

The effects of Caldolor on labour and delivery in pregnant women are unknown but, based on the known pharmacology of ibuprofen, administration is not recommended as the onset of labour may be delayed and the duration increased with a greater bleeding tendency in both mother and child (see Use in Pregnancy).

Use in Lactation

It is not known whether ibuprofen and/or its metabolites are 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 ibuprofen treatment, taking into account the importance of the drug to the mother.

Paediatric Use

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

Use in the Elderly

Clinical studies of Caldolor did not include sufficient numbers of subjects 65 years of age 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.

As with any of the NSAIDs, caution should be exercised when treating the elderly (65 years and older). In a study of hospitalized adult patients with sepsis, creatinine levels were analyzed in elderly patients (>65) receiving either 10 mg/kg (up to 800 mg) I.V. ibuprofen or placebo every 6 hours over 48 hours. There was no statistically significant difference in creatinine levels (or in % or actual change from baseline) between I.V. ibuprofen and placebo treated patients during therapy and up to 5 days after initiation of therapy [see *Clinical Studies*].

Genotoxicity

Ibuprofen was not mutagenic in bacterial gene mutation assays *in vitro* with or without metabolic activation. A weak positive response was observed in the Sister Chromatid Exchange (SCE) assay in mouse bone marrow cells at an oral dose of 270 mg/kg and at intraperitoneal doses of 50 and 100 mg/kg, with no-effect at a dose of 25 mg/kg.

Carcinogenicity

There was no evidence of carcinogenicity in mice and rats treated with ibuprofen orally at respective doses up to 100 mg/kg/day for 80 weeks and 60 mg/kg/day for two years.

Interactions with other Medicines

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 [see *Warnings and Precautions (5.2)*].

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors. Ibuprofen like other NSAIDs can reduce the antihypertensive effect of ACE inhibitors and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of thiazide diuretics and frusemide. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. The combined

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use of the three classes of drugs, thiazides, an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment.

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)*].

Lithium

Caldolor should be avoided in patients taking lithium as NSAIDs have produced elevations of plasma lithium levels and a reduction in renal lithium clearance.

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.

Corticosteroids

Increased risk of gastrointestinal bleeding.

Herbal Extracts

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

Cardiac Glycosides

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Aminoglycosides

NSAIDs may decrease the excretion of aminoglycosides.

Cyclosporine or Tacrolimus

Increased risk of nephrotoxicity when used with NSAIDs.

Mifepristone

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Quinolone antibiotics

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Zidovudine

Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and hematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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.

ADVERSE EFFECTS

The following serious adverse reactions are discussed under PRECAUTIONS:

- Cardiovascular thrombotic events
- Gastrointestinal effects
- Hepatic effects

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- Hypertension, congestive heart failure and oedema
- Renal effects
- Anaphylactoid reactions
- Serious skin reactions

The most common treatment emergent adverse effects reported in clinical studies are nausea, flatulence, vomiting, and headache. The most common reason for discontinuation of Caldolor due to adverse events in controlled trials is pruritus (<1%).

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, the rate of treatment emergent adverse effects 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, 659 patients were exposed to Caldolor, 537 in pain and 122 with fever. In the pain studies, Caldolor was started intra- or pre-operatively and administered at a dose of 400 mg or 800 mg every six hours for up to five 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 treatment emergent adverse effects listed in the following table were derived from multi-centre, controlled clinical studies in post-operative patients comparing Caldolor to placebo in patients also receiving morphine as needed for post-operative pain.

Event	Caldolor		Placebo (N=373)
	400 mg (N=134)	800 mg (N=403)	
<i>Any Reaction</i>	118 (88%)	350 (87%)	332 (89%)
Nausea	77 (57%)	205 (51%)	209 (56%)
Vomiting	30 (22%)	73 (18%)	62 (17%)
Flatulence	10 (7%)	50 (12%)	44 (12%)
Headache	12 (9%)	38 (9%)	36 (10%)
Haemorrhage	13 (10%)	13 (3%)	16 (4%)
Dizziness	8 (6%)	17 (4%)	8 (2%)
Urinary retention	7 (5%)	19 (5%)	12 (3%)
Anaemia	5 (4%)	17 (4%)	16 (4%)
Dyspepsia	6 (4%)	4 (1%)	6 (2%)
Hypokalaemia	5 (4%)	8 (2%)	11 (3%)

* All patients received concomitant morphine during these studies.

Fever Studies

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

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

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Table 5: 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	
Any Reaction	27 (87%)	25 (83%)	23 (74%)	25 (89%)
Anaemia	5 (17%)	6 (20%)	11 (36%)	4 (14%)
Eosinophilia	7 (23%)	7 (23%)	8 (26%)	7 (25%)
Hypokalaemia	4 (13%)	4 (13%)	6 (19%)	5 (18%)
Hypoproteinaemia	3 (10%)	0	4 (13%)	2 (7%)
Neutropaenia	2 (7%)	2 (7%)	4 (13%)	2 (7%)
Blood urea increased	0	0	3 (10%)	0
Hypernatraemia	2 (7%)	0	3 (10%)	0
Hypertension	0	0	3 (10%)	0
Hypoalbuminaemia	3 (10%)	1 (3%)	3 (10%)	1 (4%)
Hypotension	0	2 (7%)	3 (10%)	1 (4%)
Diarrhoea	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
Bacteraemia	4 (13%)	0	0	0

Study in Hospitalized Adult Patients with Sepsis: The incidence of treatment emergent adverse effects in hospitalized patients with severe sepsis was similar in treated and placebo patients. Patients were systematically monitored for signs of renal or bleeding complications. Analysis of changes in urine output, changes in serum creatinine, renal related adverse events, and requirement for renal dialysis were similar in both groups. Laboratory measures of platelet count, partial thromboplastin time, prothrombin time and evaluation of bleeding events, coagulation abnormalities, requirement for red cells and requirement for other blood products failed to show any clinically significant differences between I.V. ibuprofen and placebo treated subjects.

DOSAGE AND ADMINISTRATION

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 a total daily dose of 3200 mg ibuprofen. Use of the recommended maximum dose of Caldolor 800 mg every 6 hours has only been studied for a period of up to 2 days.

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

Analgesia (Pain)

Administer 400mg to 800mg of Caldolor injection by intravenous infusion every 6 hours as necessary. Caldolor must be diluted prior to administration.

Antipyretic (Fever)

Administer 400 mg of Caldolor injection by intravenous infusion, followed by 400 mg every 4 to 6 hours as necessary. Caldolor must be diluted prior to administration

Preparation and Administration

Caldolor injection **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% Glucose Injection, 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.

PRODUCT INFORMATION

Caldolor®



Visually inspect Caldolor injection 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.

Once diluted the solution should be used as soon as possible. It is a sterile solution for single use and contains no antimicrobial preservative. If storage is necessary the prepared solution should be refrigerated between 2°C and 8°C and stored for no longer than 24 hours before discarding.

Infusion time is 30 minutes.

Dosage Adjustment in Special Conditions

Renal disease

Caution is also recommended in patients with pre-existing renal disease. 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.

Hepatic impairment

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.

Gastroesophageal reflux

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.

Caldolor should be used in one patient on one occasion only. It contains no anti-microbial preservative. Unused solution should be discarded.

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 overdosage with Caldolor. There is no known antidote to ibuprofen.

In Australia, contact the Poisons Information Centre on 13 11 26 for further advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Caldolor is available in the following strengths: **400 mg in 4 mL** in a 5 mL vial (100 mg/mL) carton of 10 vials
800 mg in 8 mL in a 10 mL vial (100 mg/mL) carton of 10 vials

Store below 25°C.

Phebra product code: INJ164: 400 mg in 4 mL AUST R 175190
INJ166: 800 mg in 8 mL AUST R 175191

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

NAME AND ADDRESS OF THE SPONSOR

Phebra Pty Ltd, 332 Burns Bay Road, Lane Cove NSW 2066, Australia.
Telephone: 1800 720 020

Attachment 1: Product information for AusPAR Caldolor Ibuprofen Phebra Pty Ltd PM-2010-02393-3-1 Final 2 January 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

Caldolor[®]



POISONS SCHEDULE

Schedule 4- Prescription Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods:

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