AUSTRALIAN PRODUCT INFORMATION - CALDOLOR® (IBUPROFEN) CONCENTRATED SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ibuprofen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Caldolor concentrated injection for infusion contains the active ingredient ibuprofen.

Each 4 mL vial of Caldolor concentrated injection for infusion contains 400 mg of ibuprofen and each 8 mL vial of Caldolor concentrated injection for infusion contains 800 mg of ibuprofen. For the full list of excipients, see Section 6.1: LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

The sterile concentrated injection is a clear, colourless to slightly yellow solution and is intended for intravenous (IV) administration by infusion following dilution only.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Caldolor 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.

4.2 DOSE AND METHOD OF 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 400 mg to 800 mg of Caldolor by IV infusion every 6 hours as necessary. Caldolor is a concentrated injection for infusion that must be diluted prior to administration.

Antipyretic (Fever)
Administer 400 mg of Caldolor by IV infusion, followed by 400 mg every 4 to 6 hours as necessary.
Caldolor is a concentrated injection for infusion that must be diluted prior to administration.

Dosage Adjustment in Special Conditions

Renal Impairment

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 minimise the potential risk for an adverse GI event in patients treated with a 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.

Preparation and Administration

Caldolor concentrated injection **must be diluted** prior to intravenous (IV) infusion.

Dilute to a final concentration of 4 mg/mL or less. Appropriate diluents include 0.9% Sodium Chloride Injection USP (normal saline) or 5% Glucose Injection.

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 Caldolor for particulate matter and discolouration prior to administration, whenever solution and container permit. If visibly opaque particles, discolouration, 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.

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

4.3 CONTRAINDICATIONS

Caldolor is contraindicated in:

- Patients with known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to ibuprofen (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- For the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

- Patients with active gastrointestinal bleeding.

- Patients with spinal cord injuries.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 minimise the potential risk for an adverse CV event in patients treated with a 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 also Section 4.3 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 a 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 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 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, pharmaco-epidemiological 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 minimise the potential risk for an adverse GI event in patients treated with a 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 (see also Section 4.3 CONTRAINDICATIONS).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as Caldolor . Some of these events have been fatal or life- threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue Caldolor and evaluate the patient immediately.

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 (see also Section 4.3 CONTRAINDICATIONS).

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.

Use in Hepatic Impairment

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.

Use in Renal Impairment

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 NSAID 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.

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.

Foetal Toxicity

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including Caldolor , at about 20 weeks gestation or later in pregnancy has been associated with cases of foetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit Caldolor use to the lowest effective dose and shortest duration possible. If Caldolor treatment extends beyond 48 hours, consider ultrasound monitoring of amniotic fluid for oligohydramnios. If oligohydramnios occurs, discontinue Caldolor and follow up according to clinical practice. See Section 4.6 Use in pregnancy – Pregnancy Category C.

Premature Closure of Foetal Ductus Arteriosus:

Avoid use of NSAIDs, including Caldolor , in pregnant women at about 30 weeks gestation and later. NSAIDs, including Caldolor , increase the risk of premature closure of the foetal ductus arteriosus at approximately this gestational age. See Section 4.6 Use in pregnancy – Pregnancy Category C.

Haematological Effects

Caldolor is a concentrated injection for infusion that must be diluted prior to use (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Infusion of Caldolor without dilution can cause haemolysis.

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 haematocrit 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 also Section 4.3 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

Serious GI tract ulcerations and bleeding can occur without warning symptoms, therefore physicians should monitor for signs or symptoms of GI bleeding.

Patients on long-term treatment with NSAIDs should have full blood count (FBC) 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 .

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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation).

As with any NSAIDs, caution should be exercised when treating the elderly (65 years and older). In a study of hospitalised adult patients with sepsis, creatinine levels were analysed in elderly patients (>65) receiving either 10 mg/kg (up to 800 mg) IV 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 IV ibuprofen and placebo treated patients during therapy and up to 5 days after initiation of therapy.

PAEDIATRIC USE

Safety and effectiveness of Caldolor for management of pain and reduction of fever has not been established in paediatric patients. Caldolor should only be used in persons 18 years and over.

EFFECTS ON LABORATORY TESTS

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Aspirin

Pharmacodynamic (PD) studies have demonstrated interference with the antiplatelet activity of aspirin when ibuprofen 400 mg, given three times daily, is administered with enteric- coated low-dose aspirin. The interaction exists even following a once-daily regimen of ibuprofen 400 mg, particularly when ibuprofen is dosed prior to aspirin. The interaction is alleviated if immediate-release low-dose aspirin is dosed at least 2 hours prior to a once daily regimen of ibuprofen; however, this finding cannot be extended to enteric-coated low-dose aspirin [see Section 5.1 PHARMACODYNAMIC PROPERTIES].

Because there may be an increased risk of cardiovascular events due to the interference of ibuprofen with the antiplatelet effect of aspirin, for patients taking low-dose aspirin for cardio-protection who require analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics, where appropriate.

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.

Aminoglycosides

NSAIDs may decrease the excretion of aminoglycosides.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

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 furosemide. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. The combined 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in Renal Impairment).

Corticosteroids

Increased risk of gastrointestinal bleeding.

Ciclosporin or Tacrolimus

Increased risk of nephrotoxicity when used with NSAIDs.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Herbal Extracts

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

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.

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

Serious GI tract ulcerations and bleeding can occur without warning symptoms, therefore physicians should monitor for signs or symptoms of GI bleeding.

Patients on long-term treatment with NSAIDs should have FBC 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 .

4.6 FERTILITY, PREGNANCY AND LACTATION

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 (see also Section 4.6 Use in pregnancy – Pregnancy Category C).

Use in pregnancy - Pregnancy Category C

There are no adequate, well-controlled studies in pregnant women.

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy. Prior to week 20 of pregnancy, Caldolor should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use of NSAIDs, including Caldolor at about 20 weeks gestation or later in pregnancy has been associated with cases of foetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit Caldolor use to the lowest effective dose and shortest duration possible. If Caldolor treatment extends beyond 48 hours, consider ultrasound monitoring of amniotic fluid for oligohydramnios. If oligohydramnios occurs, discontinue Caldolor and follow up according to clinical practice

From week 30 of pregnancy, Caldolor and other NSAIDs should be avoided by pregnant women. NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause premature closure of the foetal ductus arteriosis, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth.
Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, 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.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as ibuprofen, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in foetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

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 also Section 4.6 Use in pregnancy – Pregnancy Category C).

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following serious adverse reactions are discussed under Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

- Cardiovascular thrombotic events
- Gastrointestinal effects
- Hepatic impairment
- Hypertension, congestive heart failure and oedema
- Renal impairment
- Anaphylactoid reactions Serious skin reactions
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Foetal Toxicity

The most common treatment emergent adverse effects (TEAEs) 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

Clinical trials are conducted under widely varying conditions, therefore the rate of TEAEs 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 adverse reactions occurring with oral ibuprofen are gastrointestinal.

Pain Studies

The incidence rates of TEAEs listed in Table 1 were derived from multi-centre, controlled clinical studies comparing Caldolor to placebo in patients also receiving morphine as needed for post-operative pain.

Table 1 Treatment Emergent Adverse Effects Observed in > 3% of Post-operative Patients in any Caldolor Treatment Group in Pain Studies*

Event	Caldolor		Placebo (N=373)
	400 mg (N=134)	800 mg (N=403)	
Any Reaction	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 TEAEs observed in at least two Caldolor-treated patients included abdominal pain and nasal congestion.
In hospitalised febrile patients (all causes), TEAEs observed in more than two patients in any given treatment group are presented in Table 2.

Table 2 Treatment Emergent Adverse Effects 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 Hospitalised Adult Patients with Sepsis: The incidence of TEAEs in hospitalised 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 IV ibuprofen and placebo treated subjects.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems .

4.9 OVERDOSE

The following signs and symptoms have occurred in individuals following an overdose of oral ibuprofen: abdominal pain, nausea, vomiting, drowsiness, and dizziness. In serious poisoning metabolic acidosis may occur. There are no specific measures to treat acute overdosage with Caldolor . There is no known antidote to ibuprofen.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

Clinical trials

In a healthy volunteer study, ibuprofen 400 mg given once daily, administered 2 hours prior to immediate-release aspirin (81 mg) for 6 days, showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B2 (TxB2) inhibition at 24 hours following the day-6 aspirin dose [53%]. An interaction was still observed, but minimised, when ibuprofen 400 mg given once-daily was administered as early as 8 hours prior to the immediate- release aspirin dose [90.7%]. However, there was no interaction with the antiplatelet activity of aspirin when ibuprofen 400 mg, given once daily, was administered 2 hours after (but not concomitantly, 15 min, or 30 min after) the immediate-release aspirin dose [99.2%].

In another study, where immediate-release aspirin 81 mg was administered once daily with ibuprofen 400 mg given three times daily (1, 7, and 13 hours post-aspirin dose) for 10 consecutive days, the mean % serum thromboxane B2 (TxB2) inhibition suggested no interaction with the antiplatelet activity of aspirin [98.3%]. However, there were individual subjects with serum TxB2 inhibition below 95%, with the lowest being 90.2%.

When a similarly designed study was conducted with enteric-coated aspirin, where healthy subjects were administered enteric-coated aspirin 81 mg once daily for 6 days and ibuprofen 400 mg three times daily (2, 7 and 12 h post-aspirin dose) for 6 days, there was an interaction with the antiplatelet activity at 24 hours following the day-6 aspirin dose [67%]. [see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

Analgesia (Pain)

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

In a study of patients who had undergone an elective orthopaedic surgery, 185 patients (65 men, 120 women) were randomised 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 IV 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 IV ibuprofen ($p<0.001$). In addition to experiencing less pain, patients receiving 800 mg IV ibuprofen used less morphine. In the all-treated

population, there was a 30.9% reduction in mean morphine consumption in patients receiving IV 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 IV 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 .
In a study of women who had undergone an elective abdominal hysterectomy, 319 patients were randomised to: Caldolor 800 mg, 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 (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.

Antipyretic (Fever)

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

In a multi-centre study, 120 hospitalised patients (88 men, 32 women) with temperatures of 38.3°C or greater were randomised to receive either: Caldolor (100 mg, 200 mg or 400 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 greater percentage of patients with a reduced temperature (<38.3°C) after 4 hours, compared to placebo (61%, 70%, 77% and 32%, respectively). The dose response is shown in Figure 1.

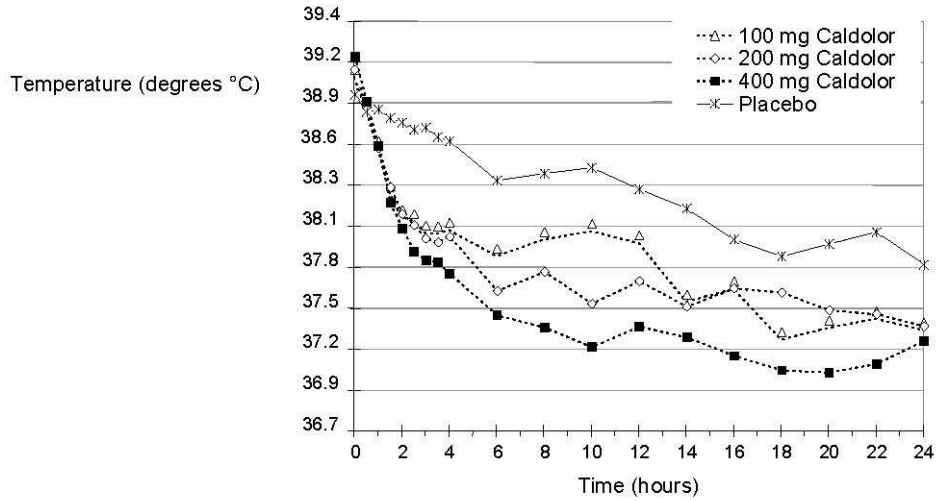


Figure 1 **Temperature Reduction by Treatment Group, Hospitalised Febrile Patients**

In a single-centre study, 60 hospitalised patients (48 men, 12 women) with uncomplicated *P. falciparum* malaria having temperatures ≥38.3°C were randomised to receive either 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 37°C *vs*. time curve for patients treated with Caldolor .

5.2 PHARMACOKINETIC PROPERTIES

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 in Table 3 and Table 4.

Table 3 Pharmacokinetic Parameters of Intravenous Ibuprofen (60 minute infusion)

	400 mg Caldolor Mean (CV%)	800 mg Caldolor Mean (CV%)
Number of subjects	12	12
AUC_{0-t} (microgram·h/mL)	109.3 (26.4)	192.8 (18.5)
C_{max} (microgram/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)

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, Tmax: time of maximum observed plasma concentrations

Table 4 Pharmacokinetic Parameters of Intravenous Ibuprofen (5-7 minute infusion) Compared to Oral Ibuprofen

	800 mg Oral Ibuprofen Mean (SD)	800 mg Caldolor Mean (SD)
Number of subjects	12	12
AUC_{0-Inf} (microgram·h/mL)	196 (36)	196 (37)
C_{max} (microgram/mL)	63 (12)	120 (13)
$T_{1/2}$ (h)	1.9 (0.3)	2.0 (0.5)
T_{max} (h)	1.5	0.11

AUC: Area-under-the-curve, C_{max}: Peak plasma concentration, SD: Standard deviation, $T_{1/2}$: Elimination half-life, T_{max}: time of maximum observed plasma concentrations

The pharmacokinetic parameters of Caldolor determined in a study with febrile patients are presented in Table 5.

Table 5 Pharmacokinetic Parameters of 400 mg Intravenous Ibuprofen (30 minute infusion) in Febrile Patients

	All Patients Mean(SD)	Critically Ill Mean (SD)	Non-Critically Ill Mean (SD)
Number of Patients	31	14	17
AUC_{0-4} (microgram.hr/mL)	70.6 (31.9)	45.9 (16.2)	87.1 (29.2)
C_{max} (microgram/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, SD: Standard deviation, $T_{1/2}$: Elimination half-life, T_{max}: time of maximum observed plasma concentrations

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

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The concentrated injection contains arginine (molar ratio of 0.92:1 arginine: ibuprofen), hydrochloric acid for pH adjustment (pH is 7.0-8.0) and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Caldolor is a concentrated injection for infusion that is supplied in a clear Type 1 glass vial, closed with a rubber stopper and an aluminium seal with a plastic flip-off cap. The stopper in the Caldolor vial does not contain natural rubber latex, dry natural rubber, or blends of natural rubber.

Caldolor is available in the following pack sizes:

400 mg in 4 mL (100 mg/mL) in a 5 mL vial: Ten (10) vials per carton

800 mg in 8 mL (100 mg/mL) in a 10 mL vial: Ten (10) vials per carton

Not all pack sizes may be available.

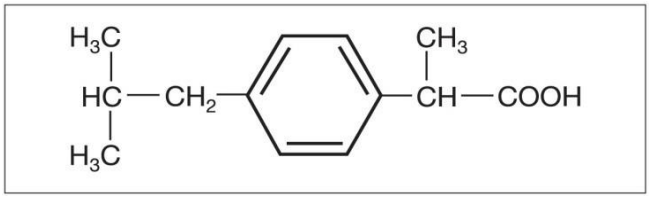
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

The molecular weight of the compound is 206.3. The molecular formula is $C_{13}H_{18}O_2$ which is (±)-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.

Chemical structure



CAS number
15687-27-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Phebra[1] Pty Ltd
19 Orion Road, Lane Cove West, NSW 2066, Australia.
Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods

AUST R 175190 (400 mg/4 mL): 12 December 2012

AUST R 175191 (800 mg/8 mL): 12 December 2012

10 DATE OF REVISION

03 April 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2,3,6.1	Editorial changes to the information
4.4	Editorial changes to precaution headings and cross references to precaution headings
4.4, 4.5	Minor editorial change
4.5	Editorial changes to comply with INN
6.5	Update on the type of glass vial used
8	Updated sponsor details

[1] Phebra and the Phi symbol are trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia. Caldolor is a registered trademark of Cumberland Pharmaceuticals Inc used under licence.