PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

IBUPROFEN ORAL SUSPENSION USP

Ibuprofen Oral Suspension USP 100 mg/ 5 mL

Suspension, 100 mg/5 mL, Oral

Analgesic / Antipyretic

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Toronto, Ontario
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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	09/2025
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	09/2025
7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests	09/2025
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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IBUPROFEN ORAL SUSPENSION USP (Ibuprofen Oral Suspension USP) is indicated for temporary relief of:

- minor aches and pains in muscles, bones and joints
- headache
- fever
- the aches and fever due to the common cold or flu, immunizations, toothache (dental pain), sore throat, earache.

1.1 Pediatrics

Pediatrics (<12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Ibuprofen in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 14.2 Study Results).

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness**.**

2 CONTRAINDICATIONS

IBUPROFEN ORAL SUSPENSION USP is contraindicated in patients:

- with active peptic ulcer or gastrointestinal bleeding, or with a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.
- who have previously exhibited hypersensitivity to it or to any ingredient in the formulation. For a complete listing of ingredients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. The potential for cross-reactivity between different nonsteroidal anti-inflammatory drugs (NSAIDs) must be kept in mind.
- with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticarial/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.
- during the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition.

- with Systemic Lupus Erythematosus as an anaphylaxis like reaction with fever may occur, particularly when ibuprofen has been administered previously. Aseptic meningitis has also been reported.
- With significant hepatic impairment or active liver disease.
- With kidney disease or severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.
- With known hyperkalemia.
- Who are taking other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects (See 9 DRUG INTERACTIONS).
- who are suffering from dehydration as a result of acute diarrhea, vomiting or lack of fluid intake.
- who are about to or recently have had heart surgery (see 7 WARNINGS AND PRECAUTIONS, Peri-Operative Considerations and 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention *(See 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Fluid and Electrolyte Balance; and 9 DRUG INTERACTIONS, Antihypertensives)*.
- Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer *(See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal and 9 DRUG INTERACTIONS, Coumarin-type)*.
- Patients at greatest risk of renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly *(See 7 WARNINGS ANDPRECAUTIONS, Renal)*.
- If urinary symptoms, hematuria and cystitis occur, the drug should be stopped immediately *(See 7 WARNINGS AND PRECAUTIONS, Genitourinary)*.
- Risk in Pregnancy: Caution should be exercised in prescribing IBUPROFEN ORAL SUSPENSION USP, if trying to conceive, during the first and second trimesters of pregnancy, or nursing. Use of NSAIDS at approximately 20 weeks of gestation or later may cause oligohydramnios, and renal dysfunction including renal failure (see *7 WARNINGS AND PRECAUTIONS*). IBUPROFEN ORAL SUSPENSION USP is CONTRAINDICATED for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) *(see 2 CONTRAINDICATIONS)*.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Do not take for fever for more than 3 days or pain for more than 5 days unless directed by a physician. Use the lowest effective dose for the shortest duration. If the painful area is red or swollen, if condition deteriorates or new symptoms occur, consult a physician.

4.2 Recommended Dose and Dosage Adjustment

Prescribed Dosage and Administration:

- Fever Reduction: For reduction of fever in children up to 12 years of age, the dosage should be adjusted on the basis of the initial temperature level. The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F (39.1°C) or 10 mg/kg if the baseline temperature is 102.5°F (39.1°C) or greater. The duration of fever reduction is generally 6 to 8 hours. The recommended maximum daily dose is 40 mg/kg.
- Analgesia: For relief of mild to moderate pain in children up to 12 years of age, the recommended dosage is 10 mg/kg, every 6 to 8 hours. The recommended maximum daily dose is 40 mg/kg. Doses should be given so as not to disturb the child's sleep pattern.
- Individualization of Dosage: The dose of IBUPROFEN ORAL SUSPENSION USP should be tailored to each patient and may be lowered or raised from the suggested doses depending on the severity of symptoms either at the time of initiating drug therapy or as the patient responds or fails to respond.
- Limited data suggests that, after the initial dose of IBUPROFEN ORAL SUSPENSION USP, subsequent doses may be lowered and still provide adequate fever control. In a situation when lower fever would require the IBUPROFEN ORAL SUSPENSION USP 5 mg/kg dose in a child with pain, the dose that will effectively treat the predominant symptom should be chosen.

OTC Dosage and Administration

- Mild to Moderate pain or fever: The OTC Dosing recommendation is based on a single dose of ibuprofen of approximately 7.5 mg/kg for either pain or fever.
- Do not use in adults.

Table 1

	Weight		Single Dose[1]
Age	lbs.	kg	Suspension: 100 mg/5 mL
0 to 3 months	6 to 11	2.5 to 5.4	--
4 to 11 months*	12 to 17	5.5 to 7.9	2.5 mL = 50 mg

Age	Weight		Single Dose[1]
	lbs.	kg	Suspension: 100 mg/5 mL
12 to 23 months*	18 to 23	8 to 10.9	3.75 mL = 75 mg
2 to 3 years	24 to 35	11 to 15.9	5 mL = 100 mg
4 to 5 years	36 to 47	16 to 21.9	7.5 mL = 150 mg
6 to 8 years	48 to 59	22 to 26.9	10 mL = 200 mg
9 to 10 years	60 to 71	27 to 31.9	12.5 mL = 250 mg
11 years	72 to 95	32 to 43.9	15 mL = 300 mg

[1]Single dose may be given every 6 to 8 hours as needed but do not exceed 4 doses per day unless advised by your doctor.
*Consumer labeling for IBUPROFEN ORAL SUSPENSION USP 100 mg/5 mL does not offer dosing for children under 2 years of age; therefore, these doses are provided as a guide for professional recommendations to consumers.

4.4 Administration

Take with food or milk if mild upset stomach occurs with use.

4.5 Missed Dose

Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip your missed dose. Do not take two doses at the same time.

5 OVERDOSAGE

Symptoms of Overdose

The toxicity of ibuprofen overdose is dependent upon the amount of drug ingested and the time elapsed since ingestion; individual responses may vary, thus making it necessary to evaluate each case separately. Although uncommon, serious toxicity and death have been reported with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other CNS symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, renal tubular acidosis, acute renal failure and apnoea (primarily in very young pediatric patients) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation, also have been reported.

Treatment of Overdose

In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption of ibuprofen when given less than 2 hours following ingestion. There is some evidence that repeated administration of activated charcoal may bind the medication that has diffused from the circulation. Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. Management of hypotension, acidosis and gastrointestinal bleeding may be necessary.

In pediatric patients, the estimated amount of ibuprofen ingested per body weight may be helpful to predict the potential for development of toxicity although each case must be evaluated. Ingestion of less than 100 mg/kg is unlikely to produce toxicity. Pediatric patients ingesting 100 to 200 mg/kg may be managed with induced emesis and a minimal observation time of at least four hours. Pediatric patients ingesting 200 to 400 mg/kg of ibuprofen should have immediate gastric emptying and at least four hours observation. Pediatric patients ingesting greater than 400 mg/kg require immediate medical referral, careful observation and appropriate supportive therapy. Induced emesis is not recommended in overdoses greater than 400 mg/kg because of the risk for convulsions and the potential for aspiration of gastric contents.

In adult patients, the dose reportedly ingested does not appear to be predictive of toxicity. The need for referral and follow-up must be judged by the circumstances at the time of the overdose ingestion. Symptomatic adults should be carefully evaluated, observed and supported.

Examples of Ibuprofen Overdose

A 41-year-old man with multiple medical problems, including long-term renal insufficiency, developed near-fatal acute renal failure after ingestion of a massive dose (36 g) of ibuprofen. He required dialysis for several months, at which point his renal function improved.

In children, ibuprofen overdoses less than 100 mg/kg are unlikely to produce toxicity. In adults, the dose of ibuprofen reportedly ingested does not appear to be predictive of toxicity.

With electrolyte replacement and other intensive measures, a 21-month-old child recovered within 5 days after accidental ingestion of 8 g of ibuprofen. A 2-year-old child who ingested approximately 8 g of ibuprofen was treated with activated charcoal, developed metabolic acidosis and acute renal insufficiency, and recovered within 72 hours. A 6-year-old child became comatose after ingesting 6 g of ibuprofen. He was treated with gastric lavage, charcoal, and various supportive measures and recovered within 24 hours.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-

844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	100 mg/5 mL IBUPROFEN ORAL SUSPENSION USP *Bubble Gum, Dye-Free Berry, Fruit Punch, Grape, Raspberry and Tropical Punch flavours in bottle of 120 mL*	**Bubble Gum Flavour:** A red-coloured oral suspension with a bubble gum aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C red No. 40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose. **Dye-Free Berry Flavour:** A white oral suspension with a berry aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose. **Fruit Punch Flavour:** A red-coloured, oral suspension with a fruit punch aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C red No. 40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified Water, sodium benzoate, sorbitol solution and sucrose. **Grape Flavour:** A purple-coloured, oral suspension with a grape aroma.

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
		Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C blue No.1 and FD&C red No. 40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose. **Raspberry Blue Flavour:** A blue-coloured oral suspension with a raspberry aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C blue No. 1, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose. **Tropical Punch Flavour:** A red-coloured oral suspension with a tropical punch aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C red No. 40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Several medical conditions which can predispose patients to the adverse effects of non-steroidal

anti-inflammatory drugs in general may be applicable to ibuprofen.

Patients taking ibuprofen should be cautioned to report to their physician unusual signs or symptoms which might be a manifestation of GI ulceration or bleeding, blurred vision or other ocular symptoms, skin rash, tinnitus, dizziness, weight gain, edema or respiratory difficulties.

Ibuprofen should be used with caution in patients with a history of cardiac failure or kidney disease because of the possibility of aggravating pre-existing states of fluid-retention or edema. Mild impairment of renal function (decreased renal blood flow and glomerular filtration rate) can occur at maximal doses of ibuprofen. Renal papillary necrosis has been reported.

Also, patients with underlying medical or pharmacologically-induced hemostatic defects could also experience further prolongation of bleeding time through the inhibition of platelet aggregation induced to varying degrees by this class of drugs.

Long-term ingestion of combinations of analgesics has been associated with the condition analgesic nephropathy. It is therefore appropriate that patients be discouraged from long-term unsupervised consumption of analgesics, particularly in combination. Patients should be directed to consult a physician if their underlying condition requires administration of ibuprofen for more than 3 days for fever or 5 days for pain, nor should ibuprofen usually be administered with acetaminophen or acetylsalicylic acid.

A general precaution seems appropriate for patients with any serious medical condition to consult a physician before using ibuprofen as an analgesic or antipyretic.

If symptoms persist or get worse, or if new symptoms occur, patients should stop use and consult a physician.

In common with other anti-inflammatory drugs, ibuprofen may mask the usual signs of infection.

Ibuprofen is NOT recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (*See 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions – Acetylsalicylic acid (ASA) or other NSAIDs*)

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY

Cardiovascular

Conditions such as congestive heart failure and hypertension may be aggravated by sodium retention and edema caused by ibuprofen in such patients.

Long term continuous use may increase the risk of heart attack or stroke.

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with dose and duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

If ibuprofen is taken in conjunction with prolonged corticosteroid therapy and it is decided to discontinue this therapy, the corticosteroid should be tapered slowly to avoid exacerbation of disease or adrenal insufficiency.

Dependence/Tolerance

Not applicable.

Ear/Nose/Throat

Patients with complete or partial syndrome of nasal polyps should not use ibuprofen (*See 2 CONTRAINDICATIONS*).

Endocrine and Metabolism

Not applicable.

Fluid and Electrolyte Balance

Fluid retention and oedema have been observed in patients treated with ibuprofen. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Ibuprofen should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with B-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Gastrointestinal

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with NSAIDs including ibuprofen.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy.

Physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months and in about 2 to 4% of patients treated for one year. The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.

IBUPROFEN ORAL SUSPENSION USP should be given under close medical supervision to patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding. Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their haemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, IBUPROFEN ORAL SUSPENSION USP should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. The major risk factors are a prior history of serious GI events and increasing age. Possible risk factors include other factors such as Helicobacter pylori infection, excess alcohol intake, smoking, female gender and concomitant oral steroid and anticoagulant, anti-coagulants, anti-platelet agents (including ASA) or selective serotonin reuptake inhibitors (SSRI's) have been associated with increased risk. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of ibuprofen therapy when and if these adverse reactions appear.

Genitourinary

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the

initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with IBUPROFEN ORAL SUSPENSION USP must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hematologic

Ibuprofen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less than that seen with acetylsalicylic acid. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatis defects, ibuprofen should be avoided by persons with intrinsic coagulation defects and by those on anticoagulant therapy.

Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur *(See 9 DRUG INTERACTIONS).*

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anaemia and agranulocytosis) associated with the use of non-steroidal anti-inflammatory drugs are rare but could occur with severe consequences.

Hepatic/Biliary/Pancreatic

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver enzyme tests (AST, ALT, ALP) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with nonsteroidal anti-inflammatory drugs. Very rarely, ibuprofen has been reported to cause vanishing bile duct syndrome. Patients should seek medical advice if they develop sudden onset abdominal pain or chronic abdominal pain associated with loss of appetite and/or jaundice and/or new onset itching.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under

strict observation.

The frequency of acute liver injury among 625,307 people who received NSAIDs in England and Wales between 1987 and 1991, was examined. There were 311,716 patients who were prescribed ibuprofen. The incidence of acute liver injury among ibuprofen users was 1.6/100,000; this was the lowest incidence among the 8 NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbrufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the presence of rheumatoid arthritis. Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Immune

Anaphylactoid reactions have occurred after administration of ibuprofen to patients with known acetylsalicylic acid or other NSAID sensitivity manifested as asthma, swelling, shock, hives, ***skin reddening***, rash, or blister. If any of these symptoms occur, patients should stop use and seek medical help right away.

Patients with complete or partial syndrome of nasal polyps, rhinitis or other allergic manifestations should not use ibuprofen or other anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals even if they have taken NSAIDs in the past without any adverse effects *(See 2 CONTRAINDICATIONS)*.

In occasional cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Monitoring and Laboratory Tests

For Monitoring and Laboratory Tests related to the use of ibuprofen see 7 WARNINGS AND PRECAUTIONS, Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal and Special populations: Geriatrics.

Pregnancy: If IBUPROFEN ORAL SUSPENSION USP is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on ibuprofen be closely monitored for amniotic fluid volume since ibuprofen may result in reduction of amniotic fluid volume and even oligohydramnios *(see 7.1 Special Populations)*.

IBUPROFEN ORAL SUSPENSION USP is CONTRAINDICATED for use in the third trimester of

pregnancy.

Neurologic

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of ibuprofen. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Tinnitus, blurred and/or diminished vision, scotoma, and/or changes in colour vision have been reported. If a patient develops such complaints while taking ibuprofen, the drug should be discontinued. Patients with any visual disturbances or eye complaints during therapy should have an ophthalmologic examination.

Peri-Operative Considerations

In general, NSAIDs should be discontinued prior to surgeries to decrease the risk of postoperative bleeding (*See 2 CONTRAINDICATIONS*).

Renal

Long term administration of nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min) are at risk. Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs. In these cases, utilisation of lower doses of ibuprofen should be considered and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps. Patients with asthma or other allergic manifestations should not use ibuprofen or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals even if they have taken NSAIDs in the past without any adverse effects *(See 2 CONTRAINDICATIONS*).

Sensitivity/Resistance

Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

Skin

Ibuprofen may cause a severe allergic reaction, especially in patients allergic to acetylsalicylic acid. Symptoms may include hives, facial swelling, asthma (wheezing), shock, skin reddening, rash or blisters with or without pyrexia or erythema. If any of these symptoms occur, patients should stop use and seek medical help right away.

Serious skin reactions such as exfoliative dermatitis, Erythema Multiforme (EM), Stevens - Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported very rarely in patients receiving ibuprofen. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue. NSAIDs should be discontinued at the first appearance of rash or any other sign of hypersensitivity

7.1 Special Populations

7.1.1 Pregnant Women

Ibuprofen is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see 2 CONTRAINDICATIONS).

Caution should be exercised in prescribing ibuprofen to women who are trying to conceive, during the first and second trimesters of pregnancy, or if breastfeeding.

Because of the known effects of NSAIDs on the fetal cardiovascular system, use of ibuprofen during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including ibuprofen, at approximately 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some more severe cases, neonatal respiratory, musculoskeletal and renal problems.

Published studies and post-marketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment, or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

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, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary anywhere from the middle (onset approximately 20 weeks) to the end of the second trimester of pregnancy, it is recommended that the use be limited to the lowest effective dose and shortest duration possible.

Consider ultrasound monitoring of fetal well-being, including of amniotic fluid volume assessment if ibuprofen treatment extends beyond 48 hours. It is recommended that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inform pregnant women not to use ibuprofen and other NSAIDs from the third trimester of pregnancy because of the risk of the premature closing of the fetal ductus arteriosus [see 2 CONTRAINDICATIONS]. If treatment with ibuprofen is needed for a pregnant woman anywhere

from the middle (onset approximately 20 weeks gestation to the end of the second trimester of pregnancy), advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

7.1.2 Breast-feeding

Nursing Women:

Pharmacokinetic studies indicated that following oral administration of ibuprofen 400 mg the level of drug which appeared in breast milk was below detection levels of 1 mcg/mL. The amount of ibuprofen to which an infant would be exposed through this source was considered negligible. However, since the absolute safety of ibuprofen ingested under these circumstances has not been determined, nursing mothers should be advised to consult a physician before using ibuprofen.

7.1.4 Geriatrics

Although ibuprofen children's oral suspension is labelled specifically for children, particular caution should be observed should it be administered to elderly patients, as they are more likely to be taking other medications or have pre-existing disease states which can increase the likelihood of the complications that have been associated with ibuprofen. Elderly patients appear to be more susceptible to the central nervous system disease reactions; cognitive dysfunction (forgetfulness, inability to concentrate, a feeling of separation from the surroundings) in such patients has been reported.

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAIDs): the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. The chance of stomach bleeding is higher if you are age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like acetylsalicylic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product. Most reports of fatal GI events are in this population. Older patients are also at risk of lower oesophageal ulceration and bleeding.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Experience reported with prescription use of ibuprofen has included the adverse reactions listed in this section. Note: Reactions listed under Causal Relationship Unknown are those where a causal relationship could not be established; however, in these rarely reported events, the possibility of a relationship to ibuprofen also cannot be excluded. The adverse reactions most frequently seen with ibuprofen therapy involve the gastrointestinal system.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

8.2.1 Clinical Trial Adverse Reactions: Pediatrics

Safety studies of ibuprofen suspension in children are among the largest prospective clinical trials ever conducted. Both the Children's Analgesic Medicine Project (CAMP) and the Boston Fever Study enrolled a wide age range of children, which supports the generalisability of these studies' findings. These large-scale studies focused on examining the potential risk in children of several rare events that can be related to the pharmacologic action of NSAIDs: GI bleeding, acute renal failure, and anaphylaxis. The Children's Analgesic Medicine Project (CAMP) was a multicenter, all-comers, open-label, prospective study to compare the safety of ibuprofen suspension with acetaminophen suspension in children with fever and/or pain. Four hundred twenty four (424) paediatricians enrolled 41,810 children (aged 1 month to 18 years old) at 69 US clinics. Safety data included information concerning medication use and adverse events summarised by severity and analysed by age groups (younger and older than 2 years). Among 30,238 children who took at least one dose of ibuprofen or acetaminophen, 14,281 were younger (< 12 years) and 15,863 were older (2 to < 12 years).

Within both age groups, the incidence rates for specific AEs, including abdominal pain, insomnia, and hyperkinesia were rare and generally 1% (in either treatment group). For older children, the only AEs with an incidence rate >1% in either group were rhinitis, pharyngitis and otitis media. AEs were generally mild to moderate for both treatments within the two age groups. There were no serious AEs, including anaphylaxis, Reye's syndrome, renal failure, GI bleeding/perforation or necrotizing fasciitis. Overall, ibuprofen exhibited an AE profile similar to acetaminophen in both younger and older children.

The Boston Fever Study was a large, randomized, double-blind study that assessed the risk of rare but serious adverse events following the use of ibuprofen suspension in febrile children between the ages of 6 months and 12 years of age. The study evaluated a total of 83,915 children enrolled by 1735 paediatricians, family physicians, and general practitioners in the U.S. Children were randomized to receive ibuprofen suspension 5 mg/kg (N=27,948), ibuprofen suspension 10 mg/kg (N=27,837) or acetaminophen suspension 12 mg/kg (N=28,130). Medications were given every 4 to 6 hours, as needed, up to five doses per day. The study focused on hospitalisations for acute GI bleeding, acute renal failure, and anaphylaxis, as well as monitoring for the occurrence of Reye syndrome. In the entire pediatric population, the authors found no significant difference between ibuprofen- and acetaminophen-treated children in the observed risk of GI bleeding, acute renal failure, or anaphylaxis. No cases of Reye syndrome were seen in febrile children.

The safety findings of the Boston Fever Study are concordant with those of the Children's Analgesic Medicine Project: ibuprofen is well tolerated in children at doses of 20 to 30 mg/kg/day and higher. No symptom or syndrome emerged in these trials that was not predictable from the drug's pharmacology or could not be anticipated based on ibuprofen's extensive use as an analgesic/antipyretic in adults.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Gastrointestinal: The generally modest elevations of serum transaminase activity that has been observed are usually without clinical sequelae but severe, potentially fatal toxic hepatitis can occur.

Renal: Renal blood flow glomerular filtration rate decreased in patients with mild impairment of renal functions who took 1200 mg/day of ibuprofen for one week. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been noted in patients treated with prescription doses (≥1200 mg/day).

Note: Reactions listed below under Causal Relationship Unknown are those which occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility of a relationship to ibuprofen cannot be excluded.

Gastrointestinal

The adverse reactions most frequently seen with prescribed ibuprofen therapy involve the gastrointestinal system.

Incidence 3 to 9%: nausea, epigastric pain, heartburn

Incidence 1 to 3%: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the gastrointestinal tract (bloating or flatulence).

Incidence less than 1%: gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal haemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase), pancreatitis, oral discomfort (local burning, sensation, irritation).

Allergic

Incidence less than 1%: anaphylaxis *(see 2 CONTRAINDICATIONS)*.

Causal relationship unknown: fever, serum sickness, lupus erythematosus.

Central Nervous System

Incidence 3 to 9%: dizziness

Incidence 1 to 3%: headache, nervousness

Incidence less than 1%: depression, insomnia

Causal relationship unknown: paresthesias, hallucinations, dream abnormalities

Aseptic meningitis and meningoencephalitis, in one case accompanied by eosinophilia in the cerebrospinal fluid, have been reported in patients who took ibuprofen intermittently and did not have any connective tissue disease, psychomotor hyperactivity.

Dermatologic

Incidence 3 to 9%: rash (including maculopapular type).

Incidence 1 to 3%: pruritus

Incidence less than 1%: vesiculobullous eruptions, urticaria, erythema multiforme, fixed eruption

Causal relationship unknown: alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP).

Cardiovascular

Incidence less than 1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure (hypertension), angioedema, myocardial infarction, stroke (cerebrovascular accident).

Causal relationship unknown: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations),

hemorrhage (non-GI), Kounis syndrome.

Special Senses

Incidence 1 to 3%: tinnitus

Incidence less than 1%: amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision). Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination.

Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

Hematologic

Incidence less than 1%: leukopenia, and decreases in haemoglobin and hematocrit.

Causal relationship unknown: haemolytic anaemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g., purpura, epistaxis, hematuria, menorrhagia).

Renal

Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia, nephritis, nephrotic syndrome, renal failure.

Like other non-steroidal anti-inflammatory drugs, ibuprofen inhibits renal prostaglandin synthesis, which may decrease renal function and cause sodium retention. Renal blood flow and glomerular filtration rate decreased in patients with mild impairment of renal function who took 1200 mg/day of ibuprofen for one week. Renal papillary necrosis has been reported. A number of factors appear to increase the risk of renal toxicity (See 7 WARNINGS AND PRECAUTIONS).

Hepatic

Incidence less than 1%: hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin, and alkaline phosphatase), vanishing bile duct syndrome.

Endocrine

Causal relationship unknown: gynecomastia, hypoglycaemic reaction.

Menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg t.i.d., for three days before menses.

Metabolic

Incidence 1 to 3%: decreased appetite, oedema, fluid retention.

Fluid retention generally responds promptly to drug discontinuation (See 7 WARNINGS AND PRECAUTIONS).

General

Incidence less than 1%: hypothermia

Respiratory

Incidence less than 1%: asthma, bronchospasms

Non-Prescription Experience: Literature (1992 to 1999) (at dosages ≤ 1200 mg/day)

One researcher conducted an extensive analysis of published data concerning the relative safety of non-prescription doses of ibuprofen and acetaminophen. Of a total of 96 randomized and blinded trials, there were 10 trials of seven days' duration or less where the safety of both drugs was directly compared. In three of these trials, the incidence of adverse events was higher with acetaminophen; there were no reported adverse events in six trials; and one trial reported a higher incidence with ibuprofen. In this subset of 10 studies, it was reported that gastrointestinal adverse events were found to be the most common type of event reported and were predominantly dyspepsia, nausea, or vomiting. None of the GI events appeared to warrant follow-up from which the author inferred there were no serious gastrointestinal events.

It was concluded: "Although we recognize that the above-mentioned data are very selective and are based on information derived from a variety of trial designs and populations, it is nonetheless instructive for indicating a relatively low incidence of severe adverse reactions with both drugs when taken at their respective non-prescription dosages."

A double-blind, placebo-controlled study (N=1246) was conducted to prospectively evaluate the gastrointestinal tolerability, as compared to placebo, of the maximum non-prescription dose and duration (1200 mg/day for 10 consecutive days) of ibuprofen use in healthy subjects representative of a non-prescription analgesic user population. Gastrointestinal adverse experiences were similar in the placebo and ibuprofen groups (67 out of 413, 16% with placebo vs. 161 out of 833, 19% with ibuprofen). There was no difference between the two groups in the proportion of discontinuing due to a gastrointestinal event. Gastrointestinal adverse experiences reported by ≥1% of subjects were: dyspepsia, abdominal pain, nausea, diarrhea, flatulence, and constipation. Seventeen (1.4%) subjects had positive occult blood tests: their frequency was comparable between treatments. When used as directed to treat episodic pain, non-prescription ibuprofen at the maximum dose of 1200 mg/day for 10 days, is well-tolerated.

In two multi-trial analyses a meta analysis, and a literature review, single doses of ibuprofen had a low incidence of gastrointestinal drug reactions, comparable to that of acetaminophen and placebo. Reports from spontaneous reporting systems in the United Kingdom, France and the United States, where a prescription is not needed for ibuprofen at a daily dose up to 1200 mg, confirm the medication's gastrointestinal safety and acceptability. A recently-completed large-scale randomized trial comparing non-prescription doses of acetylsalicylic acid, acetaminophen, and ibuprofen in 8677 adults found that the rates of significant adverse reactions were: aspirin18.7%, ibuprofen 13.7%, and acetaminophen 14.5%.

Ibuprofen was not statistically different from acetaminophen. Total gastrointestinal events (including dyspepsia) and abdominal pain were less frequent with ibuprofen (4% and 2.8%, respectively) than with acetaminophen (5.3% and 3.9%) or aspirin (7.1% and 6.8%) [all p< 0.035]. It was concluded that "The overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol and better than that of [ASA]."

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- With acetaminophen may increase the risk of adverse renal effect.
- With acetylsalicylic acid (ASA) or other NSAIDs, may result in possible additive side effects *(See 2 CONTRAINDICATIONS)*.
- With anticoagulants may increase the risk of GI adverse events (e.g., ulceration and bleeding).
- With antihypertensives the benefit and risk must be weighed individually.
- With digoxin may increase serum digoxin concentration and the risk of digoxin toxicity.
- With diuretics may reduce the diuretic effect.
- With hypoglycaemic agents (oral agents and insulin) may increase the risk of hypoglycaemia.
- With lithium may elevate plasma lithium levels, reduce renal lithium clearance and increase the risk of lithium toxicity.
- With methotrexate may increase the risk of methotrexate toxicity.

See detailed information in 9.4 Drug-Drug Interactions.

9.2 Drug Interactions Overview

Ibuprofen is not recommended for concomitant use with any other NSAIDs, including ASA.

Documented or possible drug interactions with ibuprofen include acetaminophen, digoxin, anticoagulants, oral antidiabetic agents and insulin, antihypertensives, diuretics, methotrexate, lithium and other protein-bound drugs.

A general precaution is appropriate for patients to assure the compatibility of ibuprofen with their other prescribed medications through consultation with a physician.

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential

interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Acetaminophen

Although interactions have not been reported, concurrent use with ibuprofen is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs

The use of ibuprofen in addition to any other NSAID, including ASA, is not recommended due to the absence of any evidence demonstrating synergistic benefits and the possibility of additive side effects. Animal studies show that aspirin given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been conducted.

No clinically meaningful loss of cardioprotection was observed, when patients on low dose ASA (81 mg) were administered 400 mg ibuprofen T.I.D., keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Acetylsalicylic acid (ASA) Low Dose

Ibuprofen can interfere with the anti-platelet effect of low-dose ASA (81 to 325 mg per day). Long-term daily use of ibuprofen may render ASA less effective when used for cardioprotection and stroke prevention. To minimize this interaction, regular users of ibuprofen and low-dose, immediate-release ASA should take the ibuprofen at least one hour after or 11 hours before the daily low-dose ASA. The use of delayed-release (e.g. enteric coated) ASA is not recommended when using ibuprofen regularly. Healthcare professionals should advise consumers and patients regarding the appropriate concomitant use of ibuprofen and ASA.

Antacids

A bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing aluminium hydroxide and magnesium hydroxide.

Antihypertensives

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Prostaglandins are an important factor in cardiovascular homeostasis and inhibition of their synthesis by NSAIDs may interfere with circulatory control. NSAIDs may elevate blood pressure

in patients receiving antihypertensive medication. Two meta analyses have observed this relationship for NSAIDs as a class and for certain NSAIDs in particular, but ibuprofen did not significantly affect blood pressure in either meta analysis. Consistent with this lack of effect, a study by Davies et al showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β-adrenergic blockers. Houston et al. showed no effect of three weeks' therapy with ibuprofen on the antihypertensive efficacy of verapamil, but it is not known whether this lack of interaction extends to other classes of calcium channel blockers.

When renal perfusion pressure is reduced both prostaglandins and angiotensin II are important mediators of renal autoregulation. As a class, the combination of an NSAID and angiotensin converting enzyme inhibitor theoretically may have the potential to decrease renal function. One study found a clinically significant decrease in renal function in 4 of 17 patients treated with hydrochlorothiazide and fosinopril who received ibuprofen 2400 mg/day for one month. In contrast, Minuz found no effect on the antihypertensive effect of enalapril or on plasma renin or aldosterone following two days' treatment with ibuprofen 1200 mg/day.

The relationship of ibuprofen and antihypertensives is clearly not well defined. The benefits of concomitant medication should be analysed and compared to the potential risks before being prescribed. If ibuprofen is being recommended for long-term use, then periodic monitoring of blood pressure may be useful. Blood pressure monitoring is not necessary if ibuprofen is being recommended for short-term use as an analgesic.

Coumarin-type

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of ibuprofen with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary. Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. Nevertheless, the physician should be cautious when administering ibuprofen to patients on anticoagulants

Digoxin

Ibuprofen has been shown to increase serum digoxin concentration. Increased monitoring and dosage adjustments of digitalis glycoside may be necessary during and following concurrent ibuprofen therapy.

Diuretics

Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with

ibuprofen, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Glucocorticoids:

Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

H-2 antagonists

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

Hypoglycaemic Agents

Ibuprofen may increase hypoglycaemic effects of oral antidiabetic agents and insulin.

Lithium

Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate

Ibuprofen as well as other NSAIDs has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used when ibuprofen is administered concomitantly with methotrexate.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Studies report an increased risk of gastrointestinal (GI) ulceration and bleeding when Ibuprofen as well as other NSAIDs are taken concomitantly with selective serotonin reuptake inhibitors (SSRIs) than when either class of drugs is taken alone (See 7 WARNINGS AND PRECAUTIONS – Gastrointestinal).

Other Drugs

Although ibuprofen binds extensively to plasma proteins, interactions with other protein-bound drugs occur rarely. Nevertheless, caution should be observed when other drugs, also having a high affinity for protein binding sites, are used concurrently. No interactions have been reported when ibuprofen has been used in conjunction with probenecid, thyroxine, antibiotics, cyclosporine, phenytoin, corticosteroids or benzodiazepines.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The basic mechanism of the pharmacological actions of ibuprofen, like other NSAID's, has not been precisely determined. It is generally thought to be related to the inhibition of prostaglandin synthesis.

Ibuprofen, like all nonsteroidal anti-inflammatory drugs (NSAIDs), is an analgesic, antipyretic, and anti-inflammatory medication. There is strong evidence to support the view that the main mechanism of action of ibuprofen (like other NSAIDs) is related to decreasing prostaglandin biosynthesis.

Prostaglandins are naturally-occurring fatty acid derivatives that are widely distributed in the tissues. They are believed to be a common factor in the production of pain, fever, and inflammation. Prostaglandins are believed to sensitise tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The enzyme catalysing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also known as cyclooxygenase. There is significant evidence that the main mechanism of analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition. Other pharmacologic effects such as lysosome and plasma membrane stabilisation have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

A recent study confirmed that ibuprofen 400 mg provided a significantly faster onset of relief as measured by first perceptible relief, meaningful relief, per cent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache.

10.2 Pharmacodynamics

Ibuprofen is a member of the class of agents commonly known as non-steroidal anti-inflammatory drugs (NSAID). Consistent with this classification, ibuprofen exhibits anti-inflammatory activity at higher dosage ranges. At lower adult single doses (200 to 400mg) relevant to the non-prescription analgesic/antipyretic indications and dosage strength, ibuprofen relieves pain of mild to moderate intensity and reduces fever. Clinical studies have also confirmed the analgesic and antipyretic effects of ibuprofen in children. Analogous to acetylsalicylic acid, the prototype of this class, this analgesic/antipyretic activity of ibuprofen occurs at lower doses than necessary for anti-inflammatory effects which are thought to require sustained administration of higher individual doses.

DETAILED PHARMACOLOGY

Ibuprofen

Several aspects of the pharmacokinetics of ibuprofen have been studied *in vivo* in rats, rabbits, dogs and baboons.

Studies in rats indicate that while limited absorption of ibuprofen occurs in the stomach, the principal site of absorption is the intestine. Single dose studies using C^{14} labelled ibuprofen in rats, rabbits and dogs show rapid absorption rates.

Tissue distribution studies performed in rats after both single and repeated doses of 20 mg/kg of C^{14} labelled ibuprofen demonstrate broad distribution with accumulation of radioactivity in the thyroid, adrenals, ovaries, fat and skin. Transplacental passage of ibuprofen was also noted with similar plasma levels measured in both the pregnant rats and fetuses.

Protein binding studies with plasma levels of 20 mcg/mL indicate the percent bound in rats 96%, dogs 99%, baboons 95% and humans 99%.

Four metabolites of ibuprofen have been found in the plasma of rabbits, 3 in rats, none in dogs, 2 in baboons and 2 in humans, with the liver suggested as the principal organ of metabolism. Excretion of metabolites was noted to varying degrees through both urine and feces indicating species variability in the bile and kidney excretion ratios.

While the mechanism of action of ibuprofen is not definitely known, it is generally believed to involve the inhibition of prostaglandin synthesis. Inhibition of prostaglandin biosynthesis prevents sensitization of tissues by prostaglandins to other inflammatory, pain and thermoregulatory mediators, hence accounting for the activity of ibuprofen and other nonsteroidal anti-inflammatory drugs against pain, inflammation and fever.

Inhibition of prostaglandin synthesis by ibuprofen has been demonstrated in several different experimental models: bull seminal vesicle microsomes, stomach, duodenum, kidney and brain

of the rat, microsomal preparations from rabbit brain and kidney medulla.

The analgesic efficacy of ibuprofen has been demonstrated in several animal models: phenylbenzoquinone-induced writhing in the mouse, acetylcholine-induced writhing in the mouse, the Randall-Selitto inflammed paw model in the rat, the mouse hot plate and adjuvant-induced arthritis model in the rat.

The antipyretic activity of ibuprofen has been demonstrated in yeast-induced fever in rats.

10.3 Pharmacokinetics

Absorption

Ibuprofen is rapidly absorbed after oral administration with peak plasma levels usually occurring within 1 to 2 hours. Oral absorption is estimated to be 80% of the dose. Both the rate of ibuprofen absorption and peak plasma concentrations are reduced when the drug is taken with food, but, bioavailability as measured by total area under the concentration-time curve is minimally altered.

A single 200 mg oral dose study in 6 fasting healthy men produced a peak plasma concentration of 15.0 mcg/mL at 0.75 hr. Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 ± 8.8 mcg/mL 0.5 hours after ingestion, and at 16 hours serum concentrations had dropped to 1 mcg/mL. Comparable serum levels and time to peak within 1 to 2 hours were confirmed by other investigations with 200 mg and 400 mg solid doses. A multiple dose study of administration of a 200 mg ibuprofen tablet three times a day for 2 weeks showed no evidence of accumulation of ibuprofen. As is true with most tablet and suspension formulations, ibuprofen suspension is absorbed somewhat faster than a tablet with a time to peak generally within one hour.

Distribution

Clinical studies indicate a duration of clinical effect for up to 8 hours. Ibuprofen like most drugs of its class, is highly protein bound (>99% bound at 20 mcg/mL). Based on oral dosing data there is an age- or fever-related change in volume of distribution for ibuprofen. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. The clinical significance of these findings is unknown. Tissue distribution of ibuprofen is also extensive in humans. Studies comparing synovial fluid levels with serum concentrations indicated that equilibration time post-ingestion occurred within approximately 3 to 5 hours.

Metabolism

Ibuprofen is rapidly metabolized through oxidation and glucuronic acid conjugation with urinary excretion of the inactive metabolites usually complete with 24 hours. In humans, ibuprofen is extensively metabolized with approximately 84% recoverable in the urine, primarily as conjugated hydroxyl- and carboxy- metabolites, with only approximately 1% excreted

unchanged. Less than 10% is excreted unchanged in the urine. The 2 major metabolites of ibuprofen in humans have been found to have no activity in the ultraviolet erythema test in guinea pigs and in the acetylcholine-induced mouse writhing test at doses of 10 mg/kg and 15 mg/kg respectively.

Elimination

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. It has a biphasic plasma elimination time curve with a half-life of approximately 2.0 hours. There is no difference in the observed terminal elimination rate or half-life between children and adults, however, there is an age- or fever-related change in total clearance. This suggests that the observed difference in clearance is due to differences in the volume of distribution of ibuprofen, as described above. The clinical relevance of these differences in clearance is unknown, although extensive clinical experience with ibuprofen in children at the pertinent dosage range (5 to 10 mg/kg) indicates a wide margin of safety.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of ibuprofen has also been studied in humans. Although there is little evidence of clinically significant age dependent kinetics in febrile children ages 3 months to 12 years, some differences in the pharmacokinetic parameters of volume of distribution and clearance have been observed between adults and children. Controlled clinical trials comparing doses between 5 and 10 mg/kg of ibuprofen and 10 to 15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies, there were few differences between treatments in fever reduction in the first hour and maximum fever reduction occurred between 2 and 4 hours. There was some evidence that the higher dosage range of ibuprofen (10 mg/kg) resulted in a prolonged duration of effect (from 6 to 8 hours) and that it was more effective for children with higher baseline temperatures above 102.5°F (39.1°C) but the numbers of patients were not adequate to draw definitive conclusions. In children with baseline temperatures at or below 102.5°F (39.1°C) both ibuprofen doses and acetaminophen were equally effective in their maximum effect.
- **Geriatrics:** Studies demonstrate no significant alterations in ibuprofen pharmacokinetics in the elderly or in children.
- **Hepatic Insufficiency:** Ibuprofen pharmacokinetics has also been studied in patients with alcoholic liver disease who have been assessed to have fair to poor hepatic function. Results suggest despite the liver being the primary organ of metabolism of ibuprofen, its kinetic parameters are not substantially altered by this condition.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature between 15°C to 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

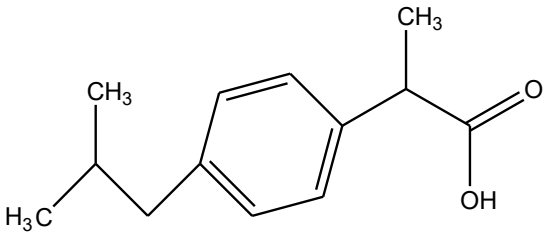
Drug Substance

Proper name: Ibuprofen

Chemical name:
1) Benzeneacetic acid, α-methyl-4- (2-methylpropyl), (±)
2) (±)-p-Isobutylhydratropic acid;
3) (±)-2-(p-Isobutylphenyl)propionic acid

Molecular formula and molecular mass: $C_{13}H_{18}O_2$; 206.3 g/mol

Structural formula:



Physicochemical properties**:**

Physical description: White crystalline powder.

Solubility: Readily soluble in alcohols, chlorinated hydrocarbon solvents, and dimethyl sulfoxide, but is only sparingly soluble in nonpolar hydrocarbon solvents.

Quantitative aqueous pH solubility profile:

Medium	pH Value	Solubility (mg/mL)
DI water	3.0	< 0.1
HCl	1.0	< 0.1
Phosphate Buffer	4.0	< 0.1
Phosphate Buffer	6.0	1.0
Phosphate Buffer	8.0	> 100

Polymorphism: Ibuprofen does not appear to exhibit genuine polymorphism.

Potential Isomerism: Ibuprofen has one chiral centre and is produced as the racemate.

pKa: 4.5 to 4.6

pH:	4.23	(Saturated solution of Ibuprofen in Carbon dioxide-free purified water.)
UV absorption maxima and molar absorptivity:	Solvents: Methanol and 0.1 N NaOH	Spectrum consists of a weak absorption band of the phenyl ring at 255 to 275nm where absorptivity is approx. 250 L/ mol·cm. Also consists of an intense band system centered around 225nm for which the molar absorptivity is approx. 9 x 10^3 L/ mol·cm
Melting range/point:	75°C to 78°C	

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of ibuprofen as an analgesic and antipyretic has been demonstrated by a variety of clinical studies and pain models.

14.2 Study Results

Dental Pain

In adults, the effects of a drug on post-surgical dental extraction pain serves as a standard model for relief of pain of mild to moderate intensity. Ibuprofen 200 mg and 400 mg has been clearly demonstrated to provide pain relief significantly superior to placebo. When compared to the "standard'' non-prescription analgesics, ibuprofen 200 mg is found to be comparable to ASA 650 mg.

Sore Throat or Ear Pain (Pediatric Models)

In children 6 to 12 years, ibuprofen 10 mg/kg was found to be effective for the relief of pain using a sore throat model, both post-op sore throat (tonsillectomy) and pharyngitis due to upper respiratory infection.

Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 12.5 mg/kg acetaminophen have been conducted in children 5 to 12 years of age with sore throat pain believed due to an infectious agent or ear pain believed due to acute otitis media. All 3 active treatments provided significant pain relief versus placebo within 1 to 2 hours of administration and had a duration of action of up to 6 hours. There were no statistically significant differences among the 3 active treatments in the degree of maximum pain relief, although the trends

favoured ibuprofen 10 mg/kg. Ibuprofen 5 mg/kg demonstrated pain relief comparable to acetaminophen 12.5 mg/kg. Ibuprofen 10 mg/kg demonstrated greater pain relief than acetaminophen 12.5 mg/kg from 3 to 6 hours after administration. A pediatric dosage schedule has been developed for ibuprofen children's oral suspension based on an ibuprofen dose of approximately 7.5 mg/kg body weight.

Dysmenorrhea

Non-steroidal anti-inflammatory drugs which inhibit prostaglandin synthesis such as ibuprofen, are particularly suitable for management of primary dysmenorrhea. Menstrual pain is now thought to result from abnormal uterine activity, which is secondary to increased production and release of endometrial prostaglandins at the time of menstruation.

Several adequate and well-controlled clinical trials provide substantial evidence of the safety and efficacy of ibuprofen at doses of 200 to 400 mg in relieving the pain of menstrual cramps.

A summary of trials of ibuprofen in the treatment of dysmenorrhea indicates the usual dose administered to be 400 mg. The few studies which are available at a 200 mg dosage indicate superiority of both ibuprofen 200 mg and 400 mg compared with ASA 650 mg.

Pain of Osteoarthritis

Several controlled clinical studies in adults provide substantial evidence of the safety and efficacy of ibuprofen at doses of 1200 mg or less per day in relieving the pain of osteoarthritis. Collectively these studies support an indication for the temporary relief of minor pains of arthritis and, in conjunction with single dose analgesia studies, support the broader indication for the temporary relief of minor aches and pains.

Headache

Ibuprofen has also been used satisfactorily in the management of headache. The efficacy of 200 mg of ibuprofen has been reported to be significantly superior to placebo and ASA 650 mg in the treatment of muscle contraction headaches. No differences in the frequency of side effects were found in the treatment groups. Similar results were reported in a study with patients referred to a Headache Clinic with frequent muscle contraction headaches.

Soft Tissue Injury

Several studies also document the efficacy of analgesic doses of ibuprofen in the treatment of soft tissue injuries such as muscular aches or athletic injuries.

Fever

Studies of its efficacy in the management of fever in adults and children demonstrate ibuprofen to be an effective antipyretic, with a duration of action of up to 8 hours when administered at a dose of 7.5 mg/kg. One controlled clinical trial comparing a single dose of ibuprofen 7.5 mg/kg with acetaminophen 12.5 mg/kg demonstrated the superiority of ibuprofen over an 8-hour

period.

14.3 Comparative Bioavailability Studies

A randomized, open-label, two-period, two-treatment, crossover comparative bioavailability study was performed using eighteen (18) healthy adult male volunteers. The rate and extent of absorption of ibuprofen was measured and compared following oral administration of the following: A single 200 mg dose of 200 mg/10 mL of IBUPROFEN ORAL SUSPENSION USP or MOTRIN Oral Suspension (under fasting conditions). The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data

Ibuprofen Oral Suspension (A single 200 mg dose: 200 mg/10 mL) From Measured Data/Fasting Conditions Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	**Ibuprofen Oral Suspension USP**	**MOTRIN®†**	**Ratio of Geometric Means (%)##**	**90% Confidence Interval (%)##**
AUC_t (mcg·h/mL)	60.2 61.5 (21)	62.5 64.4 (25)	96.3	91.61 – 101.31
AUC_{inf} (mcg·h/mL)	62.9 64.1 (20)	65.3 67.1 (24)	96.2	91.79 – 100.91
C_{max} (mcg/mL)	18.2 18.4 (14)	20.6 21.0 (21)	88.2	82.01 – 94.77
T_{max}# (h)	1.37 (61)	0.63 (59)		
T_{half}# (h)	1.84 (19)	1.89 (20)		

Arithmetic means (CV%).
Based on the least squares estimate.
† MOTRIN® is manufactured by McNeil Consumer Healthcare, Guelph, Canada, and was purchased in Canada.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Ibuprofen

Toxicity studies have been conducted using a variety of species, including: mice, rats, rabbits,

guinea pigs and beagle dogs.

Acute Toxicity Studies

Single-dose acute toxicity studies indicate that ibuprofen in lethal doses depresses the central nervous system of rodents and that large doses are ulcerogenic in both rodents and nonrodents. Ulcerogenesis may occur with both parenteral and oral administration indicating that the mechanism may have both a systemic as well as topical component.

Acute toxicity of ibuprofen in the rodent was studied in a number of models.

Single graded doses of ibuprofen were administered by oral intubation or by intraperitoneal or subcutaneous injection to groups of 10 male albino mice and male albino rats. Gross reactions were observed and mortalities recorded over a period of 14 days. The LD_{50} values determined by this method were 800 mg/kg orally and 320 mg/kg intraperitoneally in the mouse and 1600 mg/kg orally and 1300 mg/kg subcutaneously in the rat. Acute signs of poisoning were prostration in mice, and sedation, prostration, loss of righting reflex and laboured respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration.

Similar LD_{50} determinations in other strains of rats and mice are summarized in the table below.

Table 3: Acute Toxicity in Rodents (LD_{50})

Species	Route	LD_{50} Range (mg/kg)
Albino Mice	Oral Intraperitoneal	800 – 1000 320
Albino Rats	Oral Subcutaneous	1600 1300
Sprague Dawley Rat		1050
Long Evans Rat		1000

In a comparison of several non-steroidal anti-inflammatory drugs (NSAID) including ibuprofen, male rats were sacrificed and the stomachs removed and examined for ulceration either 3 or 24 hours after oral administration of various single doses of ibuprofen. Using a standard scoring technique a mean score for each dosage group was calculated and the ulcerogenic potential was expressed as a minimum ulcerogenic dose. The minimum oral ulcerogenic dose for ibuprofen in rats was calculated to be 6 to 13 mg/kg.

Another group studied the production of gastrointestinal lesions in the rat comparing ulcerogenic doses of ibuprofen and other NSAIDs after oral or intravenous administration. Both male and female Long Evans rats were used in all experiments. Prior to drug administration the animals were fasted for 8 hours. After treatment they were fed a normal diet and sacrificed

after 17 hours. Gastric and intestinal mucosa was examined for presence of ulcers. The ulcerogenic dose in 50% of treated animals (UD_{50}) was calculated. The UD_{50} following oral administration of ibuprofen was determined to be 70 mg/kg while for intravenous ibuprofen it was 210 mg/kg. The intestinal UD_{50} was 88 mg/kg following oral and 172 mg/kg with intravenous administrations. A calculated "severity index" of gastric lesions was higher by the oral than the IV route at all doses tested.

Studies of the ulcerogenic potential of ibuprofen are summarized in the table below.

Table 4: Single Dose Ulcerogenicity Studies in Rodents

Species	Route	UD_{50}* (mg/kg)	MUD** (mg/kg)
Long Evans Rat	Oral IV	70 210	50 --
Sprague Dawley Rat	Oral	--	6 - 13

*ulcerogenic dose in 50% treated animals
**minimum ulcerogenic dose

Acute toxicity has also been studied in dogs.

Various single oral doses of ibuprofen were administered to dogs with subsequent hematologic examination and biochemical analyses of blood and urine, and examination of feces for occult blood. Gross examination of the major organs occurred after the animals were sacrificed. No ill effects were seen following doses of 20 or 50 mg/kg. Oral doses of 125 mg/kg or greater produced emesis, scouring, albuminuria, fecal blood loss and erosions in the gastric antrum and pylorus.

Multiple dose ulcerogenicity studies of ibuprofen have also been conducted.

Rats were dosed by the oral route for a specific number of consecutive days, then sacrificed for examination. The ulcerogenic effect of oral ibuprofen was graded and reported by various scoring systems such as percent of animals in whom ulcers were produced by a specific dose, or the UD_{50}.

In one typical such study, Long Evans rats were administered comparative NSAIDs orally once a day for 5 days. The gastric and small intestinal mucosa were then examined for ulceration. The UD_{50}, MUD and potency ratio of the drugs tested were calculated. The minimal ulcerogenic doses of ibuprofen were 25 mg/kg for the stomach and 50 mg/kg for the intestine.

Similar studies of multiple dose ulcerogenic potential of ibuprofen are summarized in the table below.

Table 5: Multiple Oral Dose Toxicity Studies

Species	Daily Dose	Duration	Ulcerogenic Factor
Albino Rat	400 mg/kg	30 hours	Ulcers in 100%
Albino Rat		4 days	UD_{50} = 455 mg/kg/day UD_{28} = 240 mg/kg/day
Long Evans Rat		5 days	MUD = 25 – 50 mg/kg/ day
Sprague Dawley Rat	5.8 – 255 mg/kg	10 days	None
Albino Rat	7.5 mg/kg 180 mg/kg	26 weeks 26 weeks	None Ulcers in 20%
Dog	4 mg/kg 8 mg/kg 16 mg/kg	30 days 30 days 30 days	None 100% 100%

No other organ systems were generally noted to be significantly affected by these chronic administration studies. In one 30-day study, Wistar rats receiving 157 mg/kg/day ibuprofen had serum transaminase levels approximately double of those of a control, untreated group. Lower doses of ibuprofen in the same study had no significant effect on the activity of these enzymes.

Chronic toxicity studies in dogs demonstrated no gross or clinical signs of toxicity at 4, 8 or 16 mg/kg/day for 30 days. However, in all dogs given 8 or 16 mg/kg/day, postmortem examination revealed gastric ulcers or erosions. No lesions were observed in dogs given 4 mg/kg/day.

A more complete assessment of chronic toxicity of ibuprofen in dogs studied the effects of administration of oral doses of 0, 2, 4 or 26 mg/kg/day over 26 weeks. Periodic blood, urine and fecal sample analyses were performed. Histologic examination of selected organs and tissues was performed at the completion of the study. During the 26-week period, some reversible signs of gastrointestinal disturbance characterized by frequent vomiting, diarrhea, occasional passage of fresh blood and weight loss occurred in the 2 female dogs but not the males receiving 16 mg/kg ibuprofen. Occult blood was irregularly detected in fecal samples but urinalysis, liver function tests and other hematologic and blood biochemical values were not altered significantly. Gross examination of organs was normal except for ulcerative lesions in the gastrointestinal tract of organs of all dogs receiving 16 mg/kg/day. Dogs given 2 and 4 mg/kg/day suffered no adverse reactions or gastrointestinal damage.

Carcinogenicity: A study to evaluate the potential carcinogenic activity of ibuprofen involved administration of a minimum of 100 mg/kg/day to mice for 80 weeks and 60 mg/kg/day to rats for 2 years. The proportion of animals with tumours of all types examined did not differ from those in the control group. The studies confirm that in the rat and mouse, ibuprofen does not induce tumours of the liver or other organs. Further, despite prolonged treatment, no other drug-induced hepatic lesions were seen in either species.

Reproductive and Developmental Toxicology: Teratogenicity studies of ibuprofen have been conducted in rabbits and rats. Results of the experiments indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits nor is there embryotoxic or teratogenic activity in pregnant rats even when administered in ulcerogenic doses.

Effects of ibuprofen on circular strips of fetal lamb ductus arterious indicate that exposure may produce contraction of the ductus. Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Children's MOTRIN® (Ibuprofen Oral Suspension 100 mg/5 mL), Infants' MOTRIN® (Ibuprofen Oral Suspension 40 mg/10 mL) Children's/Junior Strength MOTRIN® Chewable Tablets (Ibuprofen Tablets, 50 mg and 100 mg), submission control 265393, Product Monograph, McNeil Consumer Healthcare (MAR 30, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

IBUPROFEN ORAL SUSPENSION USP

Ibuprofen Oral Suspension USP 100 mg/ 5 mL

Read this carefully before your child starts taking **IBUPROFEN ORAL SUSPENSION USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your child's medical condition and treatment and ask if there is any new information about **IBUPROFEN ORAL SUSPENSION USP.**

Serious Warnings and Precautions

- Caution in those with heart failure, high blood pressure or other conditions that may cause excess fluid collecting in tissues.
- Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you: have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like acetylsalicylic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs.
- Caution in patients at risk of kidney problems, including the elderly or those using diuretics.
- Stop use immediately if you have difficulty or pain when urinating.

What is IBUPROFEN ORAL SUSPENSION USP used for?

Up to 8 hour relief of fever

The effective, temporary relief of: Fever and temporary relief of minor aches and pains due to:

- Sore throat
- Earache
- Colds & Flu
- Headache
- Toothache
- Immunization
- Body aches, sprains and strains

How does IBUPROFEN ORAL SUSPENSION USP work?

Ibuprofen is a member of a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs work within the body by blocking the production of substances called prostaglandins,

which are involved in the development of pain and inflammation.

What are the ingredients in IBUPROFEN ORAL SUSPENSION USP?

Medicinal ingredients: Ibuprofen

Non-medicinal ingredients:

Bubble Gum Flavour: A red-coloured oral suspension with a bubble gum aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C Red No. 40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose.

Dye-Free Berry Flavour: A white oral suspension with a berry aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose.

Fruit Punch Flavour: A red-coloured, oral suspension with a fruit punch aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C Red No. 40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose.

Grape Flavour: A purple-coloured, oral suspension with a grape aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C Blue No.1 and FD&C Red No. 40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose.

Raspberry Blue Flavour: A blue-coloured oral suspension with a raspberry aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C Blue No. 1, flavour, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose.

Tropical Punch Flavour: A red-coloured oral suspension with a tropical punch aroma. Non-Medicinal Ingredients include; Carboxymethylcellulose sodium, citric acid, edetate disodium dihydrate, FD&C Red No. 40, flavour., glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution and sucrose.

IBUPROFEN ORAL SUSPENSION USP comes in the following dosage forms:

Oral suspension, 100 mg/ 5 mL

Do not use IBUPROFEN ORAL SUSPENSION USP if:

- Your child is:

- taking acetylsalicylic acid (ASA), any other nonsteroidal anti-inflammatory medication including any other ibuprofen product
- allergic/hypersensitive to ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), ASA or other salicylates, or to any of the inactive ingredients in this product (symptoms include facial or throat swelling, shortness of breath, low blood pressure)
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake.

- Your child has:
  - active or recurring stomach ulcer or gastrointestinal bleeding (bleeding in the urine or stool, or black stools)
  - Active inflammatory bowel disease (e.g. Crohn's, colitis)
  - serious liver or kidney disease
  - Systemic Lupus Erythematosus
  - high potassium in the blood
  - nasal polyps (growth inside their nose)
- Your child had or is about to have heart surgery

To help avoid side effects and ensure proper use, talk to your healthcare professional before you give IBUPROFEN ORAL SUSPENSION USP to your child. Talk about any health conditions or problems your child may have, including if your child:

- has
  - previous or current peptic ulcers
  - high blood pressure
  - heart disease or had heart failure
  - kidney or liver disease
  - asthma
  - history of gastrointestinal disease, blood clotting problems, or taking an anticoagulant
  - diabetes
- is
  - suffering from stomach pain
  - under a doctor's care for any other serious condition or is taking any other drug

Other warnings you should know about:

- Long-term continuous use may increase the risk of heart attack or stroke
- See your doctor if:
  - your child does not get any relief within 24 hours
  - redness or swelling is present in the painful area
  - your child develops any vision problems (blurred or reduced vision, colour changes occur)

Stop use and ask a doctor if

- your child has signs of stomach bleeding
- pain worsens or lasts more than 5 days
- fever worsens or lasts more than 3 days
- your child's sore throat is severe, lasts for more than 2 days or occurs with fever, headache, rash, nausea or vomiting
- any new or unusual symptoms appear

Tell your healthcare professional about all the medicines your child takes, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with IBUPROFEN ORAL SUSPENSION USP:

- coumarin-type anticoagulants
- digoxin
- diuretics (water tablets)
- lithium salt
- methotrexate
- phenytoin

How to take IBUPROFEN ORAL SUSPENSION USP:

Shake suspension well before use. Use only the enclosed measuring cup or a measured teaspoon to dose this product. Do not use any other dosing device. Measure dose with the dosage cup provided and ensure the complete dose is taken. While uncommon, if stomach upset occurs, IBUPROFEN ORAL SUSPENSION USP can be given with food or milk. If stomach upset persists, talk to your doctor.

This product does not contain directions or complete warnings for adults use. It is intended for use in children.

Usual dose:

For accurate dosing, follow the instructions carefully. Find the right dose on the chart. If possible, use weight to dose, otherwise use age.

Weight		Age	Single Oral Dose
Lb	**Kg**	**Years**	**mL**
Under 24	Under 11	Under 2	As directed by a doctor
24-35	11-15.9	2-3	5
36-47	16-21.9	4-5	7.5
48-59	22-26.9	6-8	10

Weight		Age	Single Oral Dose
Lb	Kg	Years	mL
60-71	27-31.9	9-10	12.5
72-95	32-43.9	11	15

Single dose may be repeated every 6 to 8 hours as needed. Do not exceed 4 doses of ibuprofen per day unless advised by a doctor.

Use the lowest effective dose for the shortest duration.

Overdose:

If you think you, or a person you are caring for, have taken too much IBUPROFEN ORAL SUSPENSION USP, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

What are possible side effects from using IBUPROFEN ORAL SUSPENSION USP?

These are not all the possible side effects your child may have when taking IBUPROFEN ORAL SUSPENSION USP. If your child experiences any side effects not listed here, tell your healthcare professional.

If unusual symptoms or any of the following reactions develop during treatment, stop use and see a doctor immediately:

- skin rash or itching, dizziness, any change in vision, ringing or buzzing in the ears, nausea, vomiting, sudden abdominal pain or long-term abdominal pain with the loss of appetite and/or jaundice and/or new onset of itching, diarrhea or constipation, heartburn, bloating, fluid retention, indigestion, headache, decreased appetite

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Dizziness		√	
Uncommon			
Blurred/reduced vision		√	
Vision colour changes		√	
Ringing in ears		√	
Blood in urine or stool		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Swelling of mouth, throat and extremities		√	
Difficulty breathing		√	
Chest pain		√	
Abdominal pain	√		
Severe skin rash		√	
Weight gain/fluid retention	√		
Bruising	√		

If your child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your child's daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature between 15°C to 30°C.

Keep this and all medication out of the reach of children.

Child Resistant Package

If you want more information about IBUPROFEN ORAL SUSPENSION USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website: (Drug Product Database: Access the database); the manufacturer's website (http://www.apotex.ca/products); or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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