PRODUCT MONOGRAPH

Ibuprofen Oral Suspension
USP

100 mg/5 mL

Analgesic, Antipyretic Agent – for Children

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Date of Revision:
January 6, 2021

Submission Control No. 246862

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Ibuprofen Oral Suspension USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	100 mg/5 mL ibuprofen oral suspension	None *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

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.

CONTRAINDICATIONS

Ibuprofen Oral Suspension USP should not be used in patients:

- who have previously exhibited hypersensitivity to it or to any ingredient in the formulation. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph. Ibuprofen should not be used in individuals who are known to have a sensitivity (manifested as asthma, bronchospasm, hypotension, angioedema, laryngeal edema, swelling, shock or urticaria) to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- with acute peptic ulcer or gastrointestinal bleeding.
- 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.
- who are children and 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 Peri-Operative Considerations)

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Ibuprofen use during pregnancy/nursing should be avoided (*See WARNINGS AND PRECAUTIONS, Special Populations: Pregnant Women and Nursing Women*).

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 (Arthritis Advisory Committee; 1983).

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.

Carcinogenesis and Mutagenesis

See Toxicology Section.

Cardiovascular

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

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.

Endocrine and Metabolism

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.

Gastrointestinal

Gastrointestinal side effects to ibuprofen have been reported including dyspepsia, heartburn, nausea, vomiting, anorexia, diarrhea, constipation, stomatitis, flatulence, bloating, epigastric pain, abdominal pain, and peptic ulcer with GI bleeding or perforation which could have a fatal outcome. Ibuprofen should therefore be given only under close supervision to patients with a history of upper gastrointestinal tract disease.

Occasionally serious gastrointestinal side effects have been associated with the anti-inflammatory uses of ibuprofen. Minor gastrointestinal complaints have also been reported during the clinical use of ibuprofen at analgesic doses. Therefore, if occasional and mild heartburn, upset stomach or stomach pain were to occur with its use, the administration of ibuprofen with food or milk is recommended. Patients should be advised to seek the consultation of a physician if gastrointestinal side effects occur, persist or appear to worsen.

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.

Hepatic

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 (Alam et al 1996, Basturk et al 2016; Bessone 2010; Xie et al 2018). 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.

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

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.

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.

Renal
Like other non-steroidal anti-inflammatory agents, ibuprofen inhibits renal prostaglandin synthesis which may decrease renal function and cause sodium retention.

Advanced age, hypertension, use of diuretics, diabetes, atherosclerotic cardiovascular disease, chronic renal failure, cirrhosis and conditions which may be associated with dehydration appear to increase the risk of renal toxicity. Ibuprofen should therefore be used with caution when these risk factors are present.

Respiratory
Ibuprofen may elicit an asthma attack in individuals with a history of asthma, but who have no history of allergy or asthma induced by aspirin and other NSAIDs (Antonicelli & Tagliabracci; 1995, Ayres *et al.*; 1987, Friedlander *et al.*; 1994)

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 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.

Special Populations

Pregnant Women:
No evidence specifically identifies exposure to analgesic doses of ibuprofen as a cause of harm to either mother or fetus during pregnancy (Arthritis Advisory Committee, 1983; Barry *et. al.*, 1984). Non-steroidal anti-inflammatory drugs in general, however, are known to affect the action of prostaglandin synthetase which could alter a variety of the physiological functions of prostaglandins or platelets during delivery such as facilitating uterine contraction in the mother, premature closure of the fetal ductus arteriosus which may result in persistent pulmonary hypertension in the newborn infant, and platelet-related haemostasis. Patients should therefore be advised not to use ibuprofen during pregnancy without the advice of a physician, particularly during the last trimester. Caution should be exercised in prescribing ibuprofen to women who are trying to conceive, during the first and second trimesters of pregnancy, or if nursing. Clinical information is limited on the effects of ibuprofen in pregnancy.

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 (Albert & Gernaat; 1984). 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.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Experience reported with prescription use of ibuprofen has included the following adverse reactions. Note: Reactions listed below 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.

Clinical Trial & Post-Marketing Adverse Drug 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.

Table 1 - Incidence of Adverse Events Attributed to Ibuprofen.

Adverse Effect	Incidence 3-9%	Incidence 1-3%
Gastrointestinal	• nausea • epigastric pain • heartburn	• diarrhea • abdominal distress • nausea and vomiting • indigestion • constipation • abdominal cramps and pain • gastrointestinal tract fullness (bloating or flatulence)
Central Nervous System	• dizziness	• headache • nervousness • drowsiness or somnolence
Dermatologic	• rash (including maculopapular type)	• pruritis
Special Senses		• tinnitus • asthenia
Metabolic		• decreased appetite • edema • fluid retention (generally

		responds promptly to drug discontinuation)

Less Common Adverse Drug Reactions (<1%)
Gastrointestinal: gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase), oral discomfort (local burning sensation, irritation), pancreatitis.

Blood and Lymphatic System Disorders: bone marrow toxicity

Central Nervous System: Depression, insomnia, psychomotor hyperactivity, stroke (cerebrovascular accident).

Dermatologic: vesiculobullous eruptions, urticaria, erythema, erythema multiforme, toxic epidermal necrolysis, angioedema, fixed eruption.

Special Senses: amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision).

Cardiovascular: congestive heart failure in patients with marginal cardiac function, elevated blood pressure (hypertension), myocardial infarction, hemorrhage (non-GI).

Allergic: anaphylaxis.

Hematologic: leukopenia and decreases in haemoglobin and hematocrit.

General: hypothermia

Hepatobiliary: hepatotoxicity (hepatic function abnormal, hepatitis, transaminases increased), vanishing bile duct syndrome

Renal and Urinary: nephritis, nephrotic syndrome, renal failure

Immune System: angioedema, hypersensitivity

Respiratory, Thoracic & Mediastinal: asthma, bronchospasm

Reports with an Unknown Causal Relationship
Central Nervous System: paresthesias; hallucinations; dream abnormalities; aseptic meningitis has been reported in patients with systemic lupus erythematosus or other connective tissue disease; aseptic meningitis and meningioencephalitis, in one case accompanied by eosinophilia in the cerebrospinal fluids, has been reported in patients who took ibuprofen intermittently and did not have any connective tissue disease; cognitive dysfunction has been observed in elderly patients who took ibuprofen.

Dermatologic: alopecia, Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP).

Special Senses: conjunctivitis, diplopia; optic neuritis.

Hematologic: anemia, hemolytic anemia; thrombocytopenia; granulocytopenia; bleeding episodes

(e.g. purpura, epistaxis, hematuria, menorrhagia); auto-immune hematological anemia occurred in one patient taking 400 mg of ibuprofen three times a day for ten days; fatal aplastic anemia was reported in one patient who took 600 mg per day for 8 months.
Cardiovascular: arrhythmias (sinus tachychardia, sinus bradycardia, palpitations).

Allergic: fever, serum sickness, lupus erythematosus syndrome.

Endocrine: gynecomastia; hypoglycemic reaction; menstrual delays of up to two weeks and dysfunctional uterine bleeding; occurred in nine patients taking ibuprofen 400 mg three times a day for three days before menses.

Renal: decreased creatinine clearance, polyuria, azotemia.

Abnormal Hematologic and Clinical Chemistry Findings
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.

DRUG INTERACTIONS

Overview
Although ibuprofen binds to a significant extent to plasma proteins, interactions with other protein-bound drugs occur uncommonly. Nevertheless, caution should be observed when other drugs also having a high affinity for protein binding sites are used concurrently. Some observations have suggested a potential for ibuprofen to interact with digoxin, methotrexate, phenytoin and lithium salts. However, the mechanisms and clinical significance of these observations are presently not known.

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

Drug-Drug Interactions

Coumarin Type Anticoagulants
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. However, bleeding has been reported when ibuprofen and other NSAID agents have been administered to patients on Coumarin-type anticoagulants. The use of ibuprofen in patients who are taking anticoagulants should therefore be avoided because of the possibility of enhanced GI bleeding or an additive effect due to ibuprofen's reversible anti-platelet action.

Acetylsalicylic Acid
Animal studies show that ASA given with NSAIDs, including ibuprofen yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-ASA drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of ASA on ibuprofen blood levels. Correlative clinical studies have not been done.

Since there have been no controlled trials to demonstrate whether there is any beneficial or harmful interaction with use of ibuprofen in conjunction with ASA, the combination cannot be recommended.

The platelet inhibiting effects of ibuprofen, although less potent and of shorter duration than those induced by acetylsalicylic acid, warrant cautionary supervision by a physician before co-administration of ibuprofen and anti-coagulants.

Other Anti-Inflammatory Agents (NSAIDs)
The addition of ibuprofen to a pre-existent prescribed NSAID regimen in patients with a condition such as rheumatoid arthritis may result in increased risk of adverse effects.

Diuretics
Ibuprofen, because of its fluid retention properties, can decrease the diuretic and anti-hypertensive effects of diuretics, and increased diuretic dosage may be needed. Patients with impaired renal function taking potassium-sparing diuretics who develop ibuprofen-induced renal insufficiency might be in serious danger of fatal hyperkalemia.

Acetaminophen
Although interactions have not been reported, concurrent use with ibuprofen is not advisable.

DOSAGE AND ADMINISTRATION

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 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, subsequent doses may be lowered and still provide adequate fever control (McEnvoy; 1997). In a situation when lower fever would require the ibuprofen oral suspension 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 oral suspension of approximately 7.5 mg/kg for either pain or fever.

Do not use in adults.

Table 2

Age	Weight		Single Dose[1]
	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
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 four doses per day unless advised by your doctor.
*Consumer labeling for ibuprofen oral suspension 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.

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.

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

OVERDOSAGE

Clinical Features
A clear pattern of clinical features associated with accidental or intentional overdose of ibuprofen has not been established. Reported cases of overdose have often been complicated by co-ingestions or additional suicidal gestures. The range of symptoms observed has included nausea, vomiting, abdominal pain, drowsiness, nystagmus, diplopia, headache, tinnitus, impaired renal function, coma, hypotension, lethargy, central nervous system depression, seizures, metabolic acidosis, coma, rhabdomyolysis, hypothermia, fulminant hepatic failure, apnea (primarily in very young children), cardiovascular toxicity including bradycardia, tachycardia and atrial fibrillation. A review of 4 fatalities associated with ibuprofen overdose indicates other contributing factors co-existed so it would be difficult to identify the toxicity of ibuprofen as a specific cause of death. (Barry et al.; 1984, Court *et al.*; 1984).

Post-ingestion blood levels may be useful to confirm a diagnosis and to quantify the degree of exposure but otherwise have not been helpful in predicting clinical outcome. Generally, full recovery can be expected with appropriate symptomatic management.

The following cases of overdose have been reported: A 19 month old child, 1 to ½ hours after the ingestion of 7 to 10 x 400 mg tablets of ibuprofen presented apnea, cyanosis and responded only to painful stimuli. After treatment with O_2, $NaHCO_3$, infusion of dextrose and normal saline, the child was responsive and 12 hours after ingestion appeared completely recovered. Blood levels of ibuprofen reached 102.9 mcg/mL, 8 to ½ hours after the accident. Two other children weighing

approximately 10 kg, had taken an estimated 120 mg/kg. There were no signs of acute intoxication or late sequelae. In 1 child the ibuprofen blood level at 90 minutes after ingestion was approximately 700 mcg/mL. A 19 year old male who ingested 8000 mg of ibuprofen reported dizziness and nystagmus was noted. He recovered with no reported sequelae after parenteral hydration and 3 days of bed rest.

Management of Overdose
General measures to reduce absorption such as gastric lavage, administration of activated charcoal or ipecac-induced emesis are appropriate particularly within 1 to 4 hours of ingestion. Routine symptomatic and supportive treatment is then recommended as follow-up (Court *et al.*; 1984).

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

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 (Flower *et al.*; 1985).

Pharmacodynamics
Ibuprofen: 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 (Brooks *et al.*; 1973). 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 (Cooper *et al.*; 1977, Gollardo & Rossi; 1980, Jain *et al.*; 1984, Vecchio *et al.*; 1983, Ihles; 1980) and reduces fever (Gaitonde *et al.*; 1973, Sheth *et al.*; 1973, Sheth *et al.*; 1980, Simila *et al.*; 1976). Clinical studies have also confirmed the analgesic (Bertin *et al.*; 1991, Schachtel & Thoden; 1993) and antipyretic (Walson *et al.*; 1989, Wilson *et al.*; 1991) 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 (Flower *et al.*; 1985).

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 (Adams *et al.*; 1967). 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 (Kaiser & Martin; 1978). 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 (Kaiser & Vangiessen; 1974, Glass & Swannell; 1978). 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 (Mills *et al.*; 1973). 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) (Mills *et al*.; 1973, Kober & Sjoholm; 1980). 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 (McEnvoy; 1997). 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 (Glass & Swannell; 1978).

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 (Albert & Gernaat; 1984). Less than 10% is excreted unchanged in the urine (Albert & Gernaat; 1984). 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 (Adams, Cliffe *et al*.; 1969).

Excretion: 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 (McEnvoy; 1997). 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 (Kauffman *et al*; 1989), some differences in the pharmacokinetic parameters of volume of distribution and clearance have been observed between adults and children (McEnvoy; 1997). 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 (Albert *et al*.; 1984, Kauffman *et al*.; 1989).

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 (Juhl *et al.*; 1983).

STORAGE AND STABILITY

Store at room temperature between 15ºC to 30ºC.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Ibuprofen Oral Suspension USP 120 mL bottles are available in six (6) flavours containing ibuprofen 100 mg per 5 mL as follows:

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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate and Sucrose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

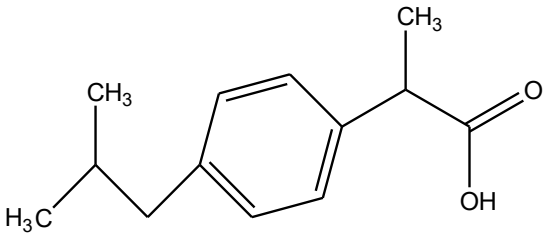
Drug Substance

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	

CLINICAL TRIALS

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 USP
(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.

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

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 (Cooper *et al*.; 1977, Cooper; 1984).

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) (Bertin *et al*.; 1991) and pharyngitis due to upper respiratory infection (Schachtel & Thoden; 1993).

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 (Molla & Donald; 1974, Shapiro & Diem; 1981, Gookin *et al*.; 1983).

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 (Dawood; 1984).

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 (Miller *et al*.; 1975, deBlecourt; 1975, Chahade *et al*.; 1976, Tylson & Glynne; 1980, Ruoff *et al*.; 1982). 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 (Vecchio *et al*.; 1983). 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 (Diamond; 1983).

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 (Muckle; 1974, Naustion; 1973).

Fever
Studies of its efficacy in the management of fever in adults and children demonstrate ibuprofen to be an effective antipyretic (Gaitonde *et al*.; 1973, Sheth *et al*.; 1980, Sinila *et al*.; 1976, Walson *et al*.; 1989, Wilson *et al*.; 1991), 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.

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 (Adams, Bough *et al.*; 1969).

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 (Adams, Bough *et al.*; 1969).

Protein binding studies with plasma levels of 20 mcg/mL indicate the percent bound in rats 96%, dogs 99%, baboons 95% and humans 99 (Mills *et al.*; 1973).

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 (Adams, Bough *et al.*; 1969, Mills *et al.*; 1973). 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 (Flower *et al.*; 1985).

Inhibition of prostaglandin synthesis by ibuprofen has been demonstrated in several different experimental models: bull seminal vesicle microsomes (Cushman & Cheung; 1976), stomach,

duodenum, kidney and brain of the rat, (Fitzpatrick & Wynaida; 1976) microsomal preparations from rabbit brain and kidney medulla (Szczeklik *et al.*; 1976)

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 (Arparicio; 1977, Adams, Cliffe *et al.*; 1969, Romer; 1980).

The antipyretic activity of ibuprofen has been demonstrated in yeast-induced fever in rats (Arparicio; 1977, Adams, Cliffe *et al.*; 1969, Romer; 1980).

MICROBIOLOGY

Not applicable.

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 (Adams & Bough *et al.*; 1969).

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

Table 4

Acute Toxicity in Rodents (LD_{50})		
Species	**Route**	**LD_{50} Range (mg/kg)**
Albino Mice[a,b]	Oral Intraperitoneal	800 – 1000 320
Albino Rats[a]	Oral Subcutaneous	1600 1300

Sprague Dawley Rat[c]		1050
Long Evans Rat[d]		1000

[a] Adams, Bough *et al*.; 1969 [b] Aparicio; 1977
[c] Fukaw a *et al*.; 1982 [d] Cioli *et al*.; 1980

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 (Atkinson & Leach; 1976). 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 (Cioli *et al.*; 1980). 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 following table:

Table 5

Single Dose Ulcerogenicity Studies in Rodents			
Species	**Route**	**UD_{50}* (mg/kg)**	**MUD** (mg/kg)**
Long Evans Rat [a]	Oral IV	70 210	50 --
Sprague Dawley Rat [b]	Oral	--	6 - 13

* UD_{50} = ulcerogenic dose in 50% treated animals
** MUD = minimum ulcerogenic dose
[a] Cioli *et al*.; 1980 [b] Atkinson & Leach; 1976

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 (Adams, Bough *et al.*; 1969). 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 (Cioli *et al.*, 1980). 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 following table:

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

[a] Parmer & Ghosh; 1981
[b] Aparicio; 1977
[c] Cioli *et al*.; 1980
[d] Paroli *et al*.; 1978
[e] Adams, Bough *et al*.; 1969

No other organ systems were generally noted to be significantly affected by these chronic administration studies. In one 30 day study (Dudkeiwicz; 1970), 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 (Adams, Bough *et al.*; 1969). 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 (Adams & Bough *et al.*; 1969). 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.

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 (Adams, Bough *et al.*; 1970). 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 tumors of the liver or other organs. Further, despite prolonged treatment, no other drug-induced hepatic lesions were seen in either species.

Teratogenicity studies of ibuprofen have been conducted in rabbits and rats (Adams, Bough *et al.*; 1969). 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 (Coceani; 1979). Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

REFERENCES

1. Adams SS, Cliffe EE, Lessel B, Nicholson JS. Some biological properties of 2-(4-isobutylphenyl)-propionic acid. J Pharm Sci 1967; 56:1686.

2. Adams SS, Bough RG, Cliffe EE, Lessel B, Mills RF. Absorption distribution and toxicity of ibuprofen. Toxicol Appl Pharmacol 1969; 15:310-330.

3. Adams SS, McCullough KF, Nicholson JS. The pharmacological properties of ibuprofen, an anti-inflammatory, analgesic and antipyretic agent. Arch Int Pharmacdyn Ther 1969; 178:115-129.

4. Adams SS, Bough RG, Cliffe EE. Some aspects of the pharmacology, metabolism and toxicology of ibuprofen. Rheumatol Phys Med 1970; 10 (Suppl 10):9-26.

5. Alam I, Ferrell LD, Bass NM. Vanishing bile duct syndrome temporally associated with ibuprofen use. Am J Gastroenterol 1996; 91: 1626-1630.

6. Arthritis Advisory Committee. Review of ibuprofen for non-prescription sale. Transcript of proceedings. Food and Drug Administration, Department of Health and Human Services, Bethesda. August 18, 1983.

7. Arthritis Drugs Advisory Committee and Nonprescription Drugs Advisory Committee. Proceedings of Joint Meeting. Centre for Drug Evaluation and Research. Department of Health and Human Services, Rockville, Maryland. March 28, 1995.

8. Albert KS, Gernaat CM. Pharmacokinetics of ibuprofen. Amer J Med 1984; 77(1A):40-46.

9. Albert KS, Gillespie WR, Wagner JG, Pau A, Lockwood GF. Effects of age on the clinical pharmacokinetics of ibuprofen. Am J Med 1984; 77(1A):47-50.

10. Antonicelli L. & Tagliabracci A. Asthma death induced by ibuprofen. Monaldi Arch Chest Dis 1995;50:276-278.

11. Aparicio L. Some aspects of the pharmacology of ibuprofen, a non-steroidal anti-inflammatory agent. Arch Int Pharmacodyn Ther 1977; 227:130-141.

12. Atkinson DC, Leach EC. Anti-inflammatory and related properties of 2-(2,4-diochlorphenoxy) phenylacetic acid (fenclofenac). Agent Actions 1976; 6:657-666.

13. Ayres J.G., Fleming D.M. & Whittington R.M. Asthma dealth due to ibuprofen (letter). Lancet 1987;I(8541):1082.

14. Barry WS, Meinzinger MM, Howse CR. Ibuprofen overdose and exposure *in utero*: results from a postmarketing voluntary reporting system. Am J Med 1984; 77(1A):47-50.

15. Basturk A, Artan R, Yılmaz A, et al. Acute vanishing bile duct syndrome after the use of ibuprofen. Arab J Gastroenterol. 2016;17(3):137-139.

16. Bertin L, Pons G, dAthis P, *et al*. Randomized, double-blind, multi-centre, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of

tonsillitis and pharyngitis in children. J. Pediatr 1991; 119:811-814.

17. Bessone F. Non-steroidal anti-inflammatory drugs: what is the actual risk of liver damage? World J Gastroenterol 2010;16(45):5651-61.

18. Brooks CD, Schlagel CA, Sikhar NC, Sobota JT. Tolerance and pharmacology of ibuprofen. Curr Ther Res 1973; 15:180-190.

19. Chahade WH, Federico WA, Joseph H, Cohen M. The evaluation of the analgesic activity and anti-inflammatory activity of ibuprofen in comparison with aspirin in patients suffering from osteoarthritis of the hips, knee and/or cervical, dorsal and/or lumbar spinal column in a double blind study. Revista Brasileria de Medicina 1976; 33:347-350.

20. Cioli V, Putzolu S, Rossi V, Corradino C. A toxicological and pharmacological study of ibuprofen guaiaicol ester (AF 2259) in the rat. Toxicol Appl Pharmacol 1980; 54:332-339.

21. Coceani F, White E, Bodach E, Olley PM. Age-dependent changes in the response of the lamb ductus areriosus to oxygen and ibuprofen. Can J Physiol Pharmacol 1979; 57:825-831.

22. Cooper SA, Needle SE, Kruger GO. Comparative analgesic potency of aspirin and ibuprofen. J Oral Surgery 1977; 35:898-903.

23. Cooper SA. Five studies on ibuprofen for postsurgical dental pain. Am J Med 1984; 77(1A):70-77.

24. Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. Adv Drug React AC Pois Rev 1984; 3:1-21.

25. Cushman DW, Cheung HS. Effect of substrate concentration on inhibition of prostaglandin synthetase of bull seminal vesicles by anti-inflammatory drugs and fenamic acid analogs. Biochim Biophys Acta 1976; 424:449-459.

26. Dawood MY. Ibuprofen and dysmenorrhea. Am J Med 1984; 77(1A):87-94.

27. deBlecourt JJ. A comparative study of ibuprofen (Brufen) and indomethacin in uncomplicated arthroses. Curr Med Res Opin 1975; 3:477-480.

28. Diamond S. Ibuprofen versus aspirin and placebo in the treatment of muscle contraction headache. Headache 1983; 23:206-210.

29. Dudkeiwicz J. Ibuprofen-induced gastrointestinal changes. Acta Physiol Pol (Poland) 1981: 32:693-701.

30. Fitzpatrick FA, Wynaida MA. *In Vivo* suppression of prostaglandin biosynthesis by non-steroidal anti-inflammatory agents. Prostaglandins 1976; 12:1037-1051.

31. Flower RJ, Moncada S, Vane JR. Analgesic-antipyretics and anti-inflammatory agents; drugs employed in the treatment of gout. In: Gilman AG, Goodman LS, Rall TW, Murad F. Goodman and Gilman's The pharmacological basis of therapeutics. Toronto: Collier MacMillan, Canada 1985; 674-689, 700-703.

32. Friedlander A.H., Friedlander I.K. & Yagiela J. Dental management of the child with developmental dyslexia. ASDC J Dent Child (United States) Jan-Feb 1994; 61:39-45.

33. Fukawa K, Kanezuka T, Ohba S, Kawano O, Hibi M, Misaki N, Sawbe T. Studies on an anti-inflammatory agent. III. Pharmacological investigations of a new non-steroidal anti-inflammatory agent: 2-OXO-3(4-(1-OXO-2-isoindolynyl)-phenyl)-butanamide (GP 650). Arzneimittelforsh 1982; 32:225-230.

34. Gaitonde BB, Dattani K, Morwani K. Antipyretic activity of ibuprofen (Brufen). J Assoc Physicians India 1973; 21:579-584.

35. Gallardo F, Rossi E. Double-blind evaluation of naproxen and ibuprofen in periodontal surgery. Pharm Ther Dent 1980; 5:69-72.

36. Glass RC, Swannell AJ. Concentrations of ibuprofen in serum and synovial fluid from patients with arthritis. Br J Clin Pharmacol 1978; 6:453-454.

37. Gookin KS, Forman ES, Vecchio TJ, Wiser WL, Morrison JC. Comparative efficacy of ibuprofen, indomethacin and placebo in the treatment of primary dysmenorrhea. South Med J 1983; 76:1361-1362, 1367.

38. Ihles JD. Relief of post-operative pain by ibuprofen: a report of two studies. Can J Surg 1980; 23:288-290.

39. Jain AK, Ryan Jr C, McMahon FD, Kuebel JO, Walters PJ, Novech C. Analgesic efficacy of low doses of ibuprofen in dental extraction pain. Clin Pharmacol Ther 1984; 35:249.

40. Juhl RP, Van Thiel DH, Dittert LW, Albert KS, Smith RB. Ibuprofen and sulindac kinetics in alcoholic liver disease. Clin Pharmacol Therap 1983; 34:104-109.

41. Kaiser DG, Martin RS. Electron-capture GLC determination of ibuprofen in serum. J Pharm Sci 1978; 67:627-630.

42. Kaiser DG, Vangiessen GJ. GLC determination of ibuprofen (+)-2-(P-isobutylphenyl) propionic acid in plasma. J Pharm Sci 1974; 63:219-221.

43. Kauffman RE, Fox B, Gupta N. Ibuprofen antipyresis and pharmacokinetics in children. Clin Pharmacol Ther 1989; 45:139 (abstract).

44. Kober A, Sjoholm I. The binding sites of human serum albumin for some non-steroidal anti-inflammatory drugs. Mol Pharmacol 1980; 8:421-426.

45. McEvoy GK, Editor. Ibuprofen. In: AFHS DI 1997. Bethesda: American Society of Health - Systems Pharmacists, 1997. p. 1499 – 1503.

46. Miller AC, Buckler JW, Sheldrake FE. Clinical studies of ibuprofen. Curr Med Res Opin 1975; 3:589-593.

47. Mills RF, Adams SS, Cliffe EE, Dickinson W, Nicholson JS. The metabolism of ibuprofen. Xenobiotica 1973: 3:589-598.

48. Molla AL, Donald JF. A comparative study of ibuprofen and paracetamol in primary dysmenorrhea. J Int Med Res 1974; 2:395-399.

49. Muckle DS. Comparative study of ibuprofen and aspirin in soft tissue injuries. Rheumatol Rehab 1974; 13:141-147.

50. Naustion AR. Study of the analgesic activities of ibuprofen compared with paracetamol. Proceeding of the 13th International Congress of Rheumatology, Kyoto, Japan 1973.

51. Parmer NS, Ghosh MN. Gastric anti-ulcer activity of (+)-cyanidanol-3, a histidine decarboxylase inhibitor. Eur J Pharmacol 1981; 69:25-32.

52. Paroli E, Nenceni P, Anania MC. Correlations of DNA, RNA and protein levels in duodenal mucosa with anti-inflammatory potency and disposition to gut damage of non-steroidal agents. Comparative behaviour of glucametacine, indomethacin, phenylbutazone and ibuprofen. Arzneimittelforsh 1978; 28:819-824.

53. Romer D. Pharmacological evaluation of mild analgesics. Br J Clin Pharmacol 1980; 10:247S-251S.

54. Ruoff G, Williams S, Cooper W, Procaccini RL. Aspirin-acetaminophen vs ibuprofen in a controlled multi-center double blind study with patients experiencing pain associated with osteoarthritis. Curr Ther Res 1982; 31:821-831.

55. Schachtel BP, Thoden WR. A placebo-controlled model for assaying systemic analgesics in children. Clin Pharmacol Ther 1993; 53:593-601.

56. Shapiro SS, Diem K. The effect of ibuprofen in the treatment of dysmenorrhea. Curr Ther Res 1981, 30:324-334.

57. Sheth UK, Gupta K, Paul T, Pispati PK. Measurement of antipyretic activity of ibuprofen and paracetamol in children. J Clin Pharmacol 1980; 20:672-675.

58. Simila S, Kouvalainen K, Keinahen S. Oral antipyretic therapy: evaluation of ibuprofen. Scand J Rheumatol 1976; 581-583.

59. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G, Ymuda A. Aspirin induced asthma: hypersensitivity to fenoprofen and ibuprofen in relation to their inhibitory action on prostaglandin generation by different microsomal enzymic preparations. J Allergy Clin Immunol 1976; 58:10-18.

60. Tylson VC, Glynne A. A comparative study of benoxaprofen and ibuprofen in osteoarthritis in general practice. J Rheumatol 1980; 7 (Suppl 6):132-138.

61. Vecchio TJ, Heilman CJ, O'Connel MJ. Efficacy of ibuprofen in muscle extraction headache. Clin Pharmacol Ther 1983; 33:199.

62. Walson PD, Galletta G, Braden NJ, *et al*. Ibuprofen, acetaminophen and placebo treatment of febrile children. Clin Pharmacol Ther 1989; 46:9-17.

63. Wilson JT, Brown RD, Kearns GL, *et al*. Single-dose, placebo controlled comparative study of ibuprofen and acetaminophen antipyresis in children. J Pediatr 1991; 119:803-811.

64. Xie W, Wang Q, Gao Y, Pan, CQ. Vanishing bile duct syndrome with hyperlipidemia after ibuprofen therapy in an adult patient: A case report. BMC Gastroenterology. 2018 18(1).

65. Product Monograph. Children's MOTRIN® Suspension; 100 mg per 5 mL; Infant Motrin® Suspension Drops, 40 mg/mL; Children's/Junior Motrin® Chewable Tablets, 50 mg and 100 mg; Junior Strength Motrin® Caplets, 100 mg. McNeil Consumer Healthcare. Date of Revision: June 18, 2020; Control number:237473.

PART III: CONSUMER INFORMATION

Ibuprofen Oral Suspension
USP

Only selected information is contained on the package label. This information is a summary and will not tell you everything about ibuprofen oral suspension. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What this medication is used for:
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

What it does:
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.

When it should not be used:
Ibuprofen oral suspension should not be used:

- if your child is taking ibuprofen, acetylsalicylic acid (ASA) or other pain or fever medication
- if your child is allergic to any of the ingredients in the product (symptoms include facial or throat swelling, shortness of breath, low blood pressure)
- if your child has peptic ulcers or gastrointestinal bleeding (bleeding in the urine or stool, or black stools)
- if your child has Systemic Lupus Erythematosus
- if your child is suffering from dehydration caused by diarrhea, vomiting or lack of fluid
- right before or after heart surgery
- in adults

What the medicinal ingredient is:
Ibuprofen

What the nonmedicinal ingredients are:
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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate 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, Sorbitol Solution, Microcrystalline Cellulose, Polysorbate 80, Purified Water, Sodium Benzoate and Sucrose.

What dosage form it comes in:
Oral suspension, 100 mg/ 5mL

WARNINGS AND PRECAUTIONS

BEFORE giving ibuprofen oral suspension to your child, talk to your doctor or pharmacist if your child:

- is dehydrated (significant fluid loss) due to continued vomiting, diarrhea or lack of fluid intake
- is suffering from stomach pain
- has peptic ulcers, high blood pressure, heart failure, serious kidney or liver disease, asthma, diabetes, or is under a doctor's care for any other serious condition or are taking any other drug
- has a history of gastrointestinal disease, blood clotting problems, or taking an anticoagulant

Also, 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's sore throat is severe, lasts for more than 2 days or occurs with fever, headache, rash, nausea or vomiting
- your child develops any vision problems (blurred or reduced vision, colour changes occur)
- any new symptoms occur

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

INTERACTIONS WITH THIS MEDICATION

Talk to your doctor if your child is taking coumarin-type anticoagulants, diuretics (water tablets), digoxin, methotrexate, phenytoin, lithium salt, as some drug interaction could occur.

PROPER USE OF THIS MEDICATION

Usual dose:
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.

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
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.

Do not use for more than 3 days for fever or 5 days for pain unless directed by a doctor. Use the lowest effective dose for the shortest duration. While uncommon, if stomach upset occurs, ibuprofen oral suspension can be given with food or milk. If stomach upset persists, talk to your doctor.

Overdose:

If you think you have taken too much Ibuprofen Oral Suspension Ibuprofen Oral Suspension, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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 or 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	
		Only if severe	In all cases
Common	Dizziness		✓
Uncommon	Blurred/ reduced vision		✓
	Vision colour changes		✓
	Ringing in ears		✓
	Blood in urine or stool		✓
	Swelling of mouth, throat and extremities		✓
	Difficulty breathing		✓
	Abdominal pain	✓	
	Severe skin rash		✓
	Weight gain / fluid retention	✓	
	Bruising	✓	

This is not a complete list of side effects. For any unexpected side effects while taking ibuprofen oral suspension, talk to your doctor or pharmacist.

HOW TO STORE IT

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

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

Child Resistant Package

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

MORE INFORMATION

If you want more information about Ibuprofen Oral Suspension:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and

includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on 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.

Last Revised: January 6, 2021