PRODUCT MONOGRAPH

CHILDREN'S IBUPROFEN SUSPENSION

Ibuprofen Oral Suspension USP

100 mg/5 mL

Analgesic/Antipyretic

Manufactured by:
Perrigo International
515 Eastern Avenue
Allegan, Michigan USA 49010

Imported by:
The Shandex Sales Group Ltd.
1100 Squires Beach Road
Pickering, Ontario Canada L1W 3N8

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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

Children's IBUPROFEN Suspension (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

Children's IBUPROFEN Suspension (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 nonsteroidal 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 nonsteroidal anti-inflammatory drugs in general may be applicable to ibuprofen.

Patients taking Children's IBUPROFEN Suspension 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.

Children's IBUPROFEN Suspension 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[1].

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 Children's IBUPROFEN Suspension for more than 3 days for fever or 5 days for pain, nor should Children's IBUPROFEN Suspension 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 Children's IBUPROFEN Suspension 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 Children's IBUPROFEN Suspension 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. Children's IBUPROFEN Suspension 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 Children's IBUPROFEN Suspension 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
Children's IBUPROFEN Suspension, 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, Children's IBUPROFEN Suspension 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[3]. 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 Children's IBUPROFEN Suspension, 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 post-operative bleeding.

Renal

Like other nonsteroidal 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. Children's IBUPROFEN Suspension 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[4-6].

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[1,7]. Nonsteroidal 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 Children's IBUPROFEN Suspension during pregnancy without the advice of a physician, particularly during the last trimester. Caution should be exercised in prescribing Children's IBUPROFEN Suspension 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 μg/mL. The amount of ibuprofen to which an infant would be exposed through this source was considered negligible[8]. 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 Children's IBUPROFEN Suspension.

Geriatrics: Although Children's IBUPROFEN 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 Reports with an Unknown Causal Relationship 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 Children's IBUPROFEN Suspension 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 Children's IBUPROFEN Suspension 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 Children's IBUPROFEN Suspension and anti-coagulants.

Other Anti-inflammatory Agents (NSAIDs): The addition of Children's IBUPROFEN Suspension 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 Children's IBUPROFEN Suspension 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 Children's IBUPROFEN 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 Children's IBUPROFEN Suspension, subsequent doses may be lowered and still provide adequate fever control[8]. In a situation when lower fever would require the Children's IBUPROFEN 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 of approximately 7.5 mg/kg for either pain or fever.

Do not use in adults.

Children: Children's IBUPROFEN Suspension

Weight		Age	Single Dose†
(lbs)	(kg)	(years)	(mL)
Under 24	Under 11	Under 2	As directed by a doctor
24 - 35	11 - 15.9	2 - 3	5 = 100 mg
36 - 47	16 - 21.9	4 - 5	7.5= 150 mg
48 - 59	22 - 26.9	6 - 8	10= 200 mg
60 - 71	27 - 31.9	9 - 10	12.5= 250 mg
72 - 95	32 - 43.9	11	15= 300 mg

† 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.

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, 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[7,10].

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, 1½ 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 µg/mL, 8½ 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 µg/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

Management of Overdose: General measures to reduce absorption such as gastric lavage, administration of activated charcoal or ipecac-induced emesis are appropriate particularly within one to four hours of ingestion. Routine symptomatic and supportive treatment is then recommended as follow-up[10].

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 NSAIDs, has not been precisely determined. It is generally thought to be related to the inhibition of prostaglandin synthesis[11].

Pharmacodynamics

Ibuprofen: Ibuprofen is a member of the class of agents commonly known as nonsteroidal anti-inflammatory drugs (NSAID). Consistent with this classification, ibuprofen exhibits anti-inflammatory activity at higher dosage ranges[12]. At lower adult single doses (200-400 mg) relevant to the non-prescription analgesic/antipyretic indications and dosage strength, ibuprofen relieves pain of mild to moderate intensity[13-17] and reduces fever[18-20]. Clinical studies have also confirmed the analgesic[21,22] and antipyretic[23,24] 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[11].

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 µg/mL at 0.75 hr[35]. Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 ±8.8 µg/mL 0.5 hours after ingestion, and at 16 hours serum concentrations had dropped to 1 µg/mL[37]. Comparable serum levels and time to peak within 1-2 hours were confirmed by other investigations with 200 mg and 400 mg solid doses[38,39]. 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[40]. As is true with most tablet and suspension formulations, ibuprofen oral 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 µg/mL)[30,40]. 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[8]. 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[39].

Metabolism: Ibuprofen is rapidly metabolized through oxidation and glucuronic acid conjugation with urinary excretion of the inactive metabolites usually complete within 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[8]. Less than 10% is excreted unchanged in the urine[8]. 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[29].

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[9]. 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 (5-10 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[26], some differences in the pharmacokinetic parameters of volume of distribution and clearance have been observed between adults and children[9]. Controlled clinical trials comparing doses between 5 and 10 mg/kg of ibuprofen and 10-15 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 children[25,26].

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[27].

STORAGE AND STABILITY

Store at controlled room temperature (15-30°C).
Protect from high humidity and excessive heat.
Keep out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Children's IBUPROFEN Suspension is available in Bubblegum, Grape and Dye-Free Berry flavours in bottles of 120 mL and 240 mL.

Medicinal Ingredient: 100 mg/5 mL Ibuprofen

Non-Medicinal Ingredients:

Bubblegum Flavour: Anhydrous Citric Acid, FD&C Red #40, Flavour, Glycerin, High Fructose Corn Syrup, Hypromellose, Polysorbate 80, Purified Water, Sodium Benzoate, Sorbitol Solution, Xanthan Gum

Grape Flavour: Anhydrous Citric Acid, D&C Red #33, FD&C Blue #1, FD&C Red #40,

Flavour, Glycerin, High Fructose Corn Syrup, Hypromellose, Polysorbate 80, Purified Water, Sodium Benzoate, Sorbitol Solution, Xanthan Gum

Dye-Free Berry Flavour: Anhydrous Citric Acid, Flavour, Glycerin, High Fructose Corn Syrup, Hypromellose, Polysorbate 80, Purified Water, Sodium Benzoate, Sorbitol Solution, Xanthan Gum

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

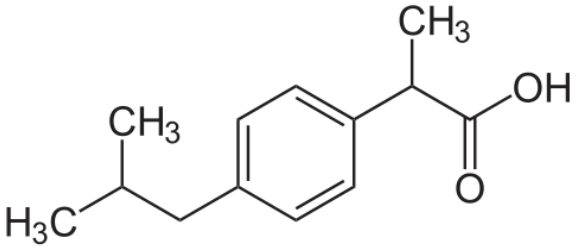
Drug Substance

Proper name: Ibuprofen

Chemical name: (±)-2-(p-isobutylphenyl) propionic acid

Molecular formula and molecular mass: $C_{13}H_{18}O_2$ 206.28

Structural formula:



Physicochemical properties:

- White crystalline powder with a characteristic odour and slight taste.
- Very slightly soluble in water and very soluble in alcohol and other common organic solvents.
- Apparent pK_a 5.2.
- Melting point is 75°C to 75.5°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single center, bioequivalence, blinded, single-dose, randomized, 2-way crossover study, performed under fasting conditions was completed using Children's IBUPROFEN Suspension and Children's MOTRIN Suspension 100 mg/5 mL administered as a 10 mL x 100 mg/5 mL (for a total dose of 200 mg) to 24 healthy adults. Results from this comparative bioavailability study are presented in the table below:

Table 2: Results from Comparative Bioavailability Study

Ibuprofen
(10 mL x 100 mg/5 mL)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	% Confidence Interval
AUC_T (ng•h/mL)	59872.36 60916.17 (19.20)	59045.68 60041.64 (19.16)	101.40	97.57 – 105.38
AUC_I (ng•h/mL)	60692.05 61749.50 (19.15)	59824.22 60827.38 (19.10)	101.45	97.67 – 105.38
C_{MAX} (ng/mL)	19742.47 20212.60 (22.24)	19182.80 19556.48 (21.76)	102.92	96.93 – 109.27
T_{MAX}§ (h)	0.694 (47.13)	0.892 (74.94)		
$T_{½}$§ (h)	1.99 (11.99)	1.97 (12.77)		

* Children's IBUPROFEN Suspension manufactured by Perrigo International (USA).
† Children's MOTRIN Suspension manufactured by McNeil Consumer Healthcare (Canada).
§ Expressed as the arithmetic mean (CV%) only.

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[13,41].

Sore Throat or Ear Pain (Pediatric Models): In children 6-12 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)[21] and pharyngitis due to upper respiratory infection[22].

Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 12.5 mg/kg acetaminophen have been conducted in children 5-12 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 Children's IBUPROFEN Suspension based on an ibuprofen dose of approximately 7.5 mg/kg body weight.

Dysmenorrhea: Nonsteroidal 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 mg to 400 mg in relieving the pain of menstrual cramps[42-44].

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[45].

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[46-50]. 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[16]. 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[51].

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[52,53].

Fever: Studies of its efficacy in the management of fever in adults and children demonstrate ibuprofen to be an effective antipyretic,[18-20,23,24] 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[28,29].

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[28,29].

Protein binding studies with plasma levels of 20 μg/mL indicate the percent bound in rats 96%, dogs 99%, baboons 95% and human 99%[30].

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[28,30]. 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[11].

Inhibition of prostaglandin synthesis by ibuprofen has been demonstrated in several different experimental models: bull seminal vesicle microsomes,[31] stomach, duodenum, kidney and brain of the rat,[32] microsomal preparations from rabbit brain and kidney medulla[33].

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[34-36].

The antipyretic activity of ibuprofen has been demonstrated in yeast-induced fever in rats[34-36].

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 a 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[2].

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[28,29,34]	Oral Intraperitoneal	800-1000 320
Albino Rats[28,29]	Oral Subcutaneous	1600 1300
Sprague Dawley Rat[54]		1050
Long Evans Rat[55]		1000

In a comparison of several nonsteroidal 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[56]. 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 6-13 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[55]. 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 the 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[55]	Oral	70	50
	IV	210	-
Sprague Dawley Rat[56]	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[29]. 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[55]. 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 (mg/kg)	Duration	Ulcerogenic Factor
Albino Rat[57]	400	30 hours	Ulcers in 100%
Albino Rat[34]		4 days	UD_{50} = 455 mg/kg/day UD_{28} = 240 mg/kg/day
Long Evans Rat[55]		5 days	MUD = 25-50 mg/kg/day
Sprague Dawley Rat[58]	5.8-225	10 days	None
Albino Rat[28,29]	7.5 180	26 weeks 26 weeks	None Ulcers in 20%
Dog[28,29]	4 8 16	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[59], 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[28,29]. 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[28,29]. Periodic blood, urine and fecal sample analyses was performed. Histologic examination of selected organs and tissues were 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[60]. 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.

Teratogenicity studies of ibuprofen have been conducted in rabbits and rats[28,29]. 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[61]. Such an effect might be anticipated because of the known prostaglandin inhibiting properties of ibuprofen.

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62. Children's Motrin Suspension (Ibuprofen Oral Suspension McNeil Std.) 100 mg/5 mL. McNeil Consumer Healthcare. June 18, 2020.

PART III: CONSUMER INFORMATION
Children's IBUPROFEN Suspension
Ibuprofen Oral Suspension USP

This leaflet is part III of a three-part "Product Monograph" published when Children's IBUPROFEN Suspension was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Children's IBUPROFEN Suspension. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
The effective, temporarily 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 nonsteroidal 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:
Children's IBUPROFEN 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 important nonmedicinal ingredients are:
See Inactive ingredients section of outer product carton.

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

WARNINGS AND PRECAUTIONS

BEFORE you use Children's IBUPROFEN Suspension, 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 interactions could occur.

PROPER USE OF THIS MEDICATION

Usual dose:
Shake suspension well before use. Use only the enclosed dosage cup. 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 Dose†
(lbs)	(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 given every 6 to 8 hours as needed but do not exceed 4 doses per day unless advised by your doctor.

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.

Overdose:

In case of drug overdose, contact a health care practitioner, 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, abdominal pain or cramps, diarrhea or constipation, heartburn, bloating, fluid retention, indigestion, headache, decreased appetite.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		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 effects while taking Children's IBUPROFEN Suspension, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature (15-30°C).

Protect from high humidity and excessive heat.

Keep out of the reach of children.

Child-resistant package.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **-Fax toll-free to 1-866-678-6789, or**
  - **-Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Perrigo International, at: 1-800-719-9260

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