PRODUCT MONOGRAPH

CHILDREN'S ADVIL® CHEWABLE TABLETS

Ibuprofen Tablets USP, 50 mg

CHILDREN'S ADVIL®
CHILDREN'S ADVIL® FEVER FROM COLDS OR FLU

Ibuprofen 100 mg/5 mL
Ibuprofen Oral Suspension, USP

JUNIOR STRENGTH ADVIL®
JUNIOR STRENGTH ADVIL® FEVER FROM COLDS OR FLU

Ibuprofen Tablets USP, 100 mg

ADVIL® PEDIATRIC DROPS
ADVIL® PEDIATRIC DROPS FEVER FROM COLDS OR FLU

Ibuprofen 40 mg/mL
Ibuprofen Oral Suspension, USP

Analgesic/Antipyretic

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CHILDREN'S ADVIL®
CHILDREN'S ADVIL® FEVER FROM COLDS OR FLU
ADVIL® PEDIATRIC DROPS
ADVIL® PEDIATRIC DROPS FEVER FROM COLDS OR FLU

Ibuprofen Oral Suspension USP

CHILDREN'S ADVIL CHEWABLE TABLETS
JUNIOR STRENGTH ADVIL®
JUNIOR STRENGTH ADVIL® FEVER FROM COLDS OR FLU

Ibuprofen Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Children's Advil® Chewable Tablets: Ibuprofen Tablets 50 mg Children's Advil® and Children's Advil® Fever from Colds or Flu : 100 mg/5 mL ibuprofen oral suspension Junior Strength Advil® and Junior Strength Advil Fever from Colds or Flu : Ibuprofen Tablets 100 mg Advil® Pediatric Drops and Advil® Pediatric Drops Fever from Colds or Flu: 40 mg/ mL ibuprofen oral suspension	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil® and Junior Strength Advil® Fever from Colds or Flu (ibuprofen) are indicated for:

- Fever and pain due to colds or flu, sore throat, immunization and earache.

Advil® Pediatric Drops and Advil® Pediatric Drops Fever from Colds or Flu (ibuprofen) are indicated for:

- Fever and pain due to colds, sore throat, immunization, and earache

Geriatrics (>65 years of age):
Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections (See *Warnings and Precautions*).

Pediatrics (<12 years of age):
Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil® and Junior Strength Advil® Fever from Colds or Flu are indicated for children 2-12 years of age. Advil® Pediatric Drops and Advil® Pediatric Drops Fever from Colds or Flu are indicated for infants and children 4 months to 3 years of age.

CONTRAINDICATIONS

- Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

- Known or suspected hypersensitivity to the drug or other non-steroidal anti-inflammatory drugs. Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. The potential for cross-reactivity between different nonsteriodal anti-inflammatory drugs (NSAIDs) must be kept in mind.

    - Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil Pediatric Drops Fever from Colds or Flu should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by

ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

- Significant hepatic impairment or active liver disease.
- Children who have suffered significant fluid loss due to vomiting, diarrhea or lack of fluid intake, should not be given ibuprofen.
- Ibuprofen is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.
- Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.
- Ibuprofen should not be used during the third trimester of pregnancy.
- Ibuprofen is contraindicated in patients with systemic lupus erythematosus, as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.
- Ibuprofen should not be used in the presence of known hyperkalemia (also see Warnings and Precautions - Renal section).
- Do not use right before or after heart surgery.

Serious Warnings and Precautions

- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See *WARNINGS AND PRECAUTIONS, Cardiovascular* and *Fluid and Electrolyte Balance; and DRUG INTERACTIONS, Antihypertensives*).
- Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer (See *WARNINGS AND PRECAUTIONS, Gastrointestinal* and *DRUG INTERACTIONS, Coumarin-type anticoagulants*).
- Patients at greatest risk of renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly (See *WARNINGS AND PRECAUTIONS, Renal*).
- If urinary symptoms, hematuria and cystitis occur, the drug should be stopped immediately (See *WARNINGS AND PRECAUTIONS, Genitourinary*).
- Ibuprofen use during pregnancy/nursing should be avoided (See *WARNINGS AND PRECAUTIONS, Special Populations: Pregnant Women and Nursing Women). >*

WARNINGS AND PRECAUTIONS

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

Carcinogenesis and Mutagenesis
Not applicable

Cardiovascular
Use of ibuprofen may precipitate congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations.

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400 mg or more daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for e.g., myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g., ≤1200 mg daily) is associated with an increased risk of myocardial infarction.[116,117]
Long term continuous use may increase the risk of heart attack or stroke.

Dependence/Tolerance
Not applicable.

Ear/Nose/Throat
Patients with complete or partial syndrome of nasal polyps should not use Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu (See *Contraindications*).

Endocrine and Metabolism
Not applicable.

Fluid and Electrolyte Balance
Fluid retention and oedema have been observed in patients treated with ibuprofen. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Children's Advil®, Children's Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

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

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

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

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

Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu should be given under close medical supervision to patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract

such as ulcerative colitis and Crohn's disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

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

If ulceration is suspected or confirmed, or if GI bleeding occurs, Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

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

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or or whether Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu therapy should be discontinued when and if these adverse reactions appear.

Genitourinary

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hematologic

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action such as those on anti-coagulants or suffering from haemophillia or platelet disorders should be carefully observed when ibuprofen is administered. Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur. (See Drug Interactions)

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

Hepatic/Biliary/Pancreatic

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests 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 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.

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

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

The frequency of acute liver injury among 625,307 people who received NSAIDs in England and Wales between 1987 and 1991, was examined.[68] There were 311,716 patients who were prescribed ibuprofen. The incidence of acute liver injury among ibuprofen users was 1.6/100,000; this was the lowest incidence among the 8 NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbrufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the presence of rheumatoid arthritis. Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Immune

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

Neurologic

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

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of ibuprofen and other non-steroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time. Patients with glaucoma should not use Children's Advil, Children's Advil Fever from Colds or Flu, Children's Advil Chewable Tablets, Junior Strength Advil, Junior Strength Advil Fever from Colds or Flu, Advil Pediatric Drops or Advil Pediatric Drops Fever from Colds or Flu.

Peri-Operative Considerations

In general, NSAIDs are discontinued prior to surgeries to decrease the risk of post-operative bleeding.

Psychiatric

See *Warnings and Precautions, Neurologic.*

Renal

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

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

Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilisation of

lower doses of Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu should be considered and patients carefully monitored.

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

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

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

Sexual Function/Reproduction
Not applicable.

Skin
In rare cases, serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms), AGEP (Acute Generalized Exanthematous Pustulosis) and erythema multiforme) have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue. NSAIDs should be discontinued at the first appearance of rash or any other sign of hypersensitivity

Special Populations

Pregnant Women:

Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of

premature closure of the ductus arteriosus and the potential to prolong parturition (see Toxicology).

Caution should be exercised in prescribing these products to women who are trying to conceive, during the first and second trimesters of pregnancy, or if breastfeeding (see Toxicology).

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. Because of the known effects of NSAIDs on the fetal cardiovascular system, use of ibuprofen during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy.

Nursing Women: The high protein binding and lower pH of breast milk versus plasma tend to inhibit the excretion of ibuprofen into breast milk.[8] One study showed an ibuprofen concentration of 13 ng/mL 30 minutes after ingesting 400 mg.[18] The milk:plasma ratio was 1:126. This translates to an infant exposure of 0.0008% of the maternal dose. It is not known to what extent, if any, ibuprofen crosses the human placenta.

Pediatrics: Studies conducted to date have not demonstrated pediatric-specific problems that would limit the usefulness of ibuprofen in children 4 months and older.

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

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Monitoring and Laboratory Tests

For *Warnings and Precautions* related to the use of Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu and Monitoring and Laboratory Tests see *Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal and Subpopulations: Elderly*.

ADVERSE REACTIONS

Clinical Trial 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.

Experience in Children

Safety studies of ibuprofen suspension in children are among the largest prospective clinical trials ever conducted. Both the Children's Analgesic Medicine Project (CAMP)[93] and the Boston Fever Study [94-96] enrolled a wide age range of children, which supports the generalisability of these studies' findings. These large-scale studies focused on examining the potential risk in children of several rare events that can be related to the pharmacologic action of NSAIDs: GI bleeding, acute renal failure, and anaphylaxis. The Children's Analgesic Medicine Project (CAMP) was a multicenter, all-comers, open-label, prospective study to compare the safety of ibuprofen suspension with acetaminophen suspension in children with fever and/or pain.[93] Four hundred twenty four (424) paediatricians enrolled 41,810 children (aged 1 month to 18 years old) at 69 US clinics. Safety data included information concerning medication use and adverse events summarised by severity and analysed by age groups (younger and older than 2 years). Among 30,238 children who took at least one dose of ibuprofen or acetaminophen, 14,281 were younger (<2 years) and 15,863 were older (2 - < 12 years).

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

The Boston Fever Study[94-96] was a large, randomized, double-blind study that assessed the risk of rare but serious adverse events following the use of ibuprofen suspension in febrile children between the ages of 6 months and 12 years of age. The study evaluated a total of 83,915 children enrolled by 1735 paediatricians, family physicians, and general practitioners in the U.S. Children were randomized to receive ibuprofen suspension 5 mg/kg (N=27,948), ibuprofen suspension 10 mg/kg (N=27,837) or acetaminophen suspension 12 mg/kg (N=28,130). Medications were given every 4-6 hours, as needed, up to five doses per day. The study focused

on hospitalisations for acute GI bleeding, acute renal failure, and anaphylaxis, as well as monitoring for the occurrence of Reye syndrome. In the entire pediatric population, the authors found no significant difference between ibuprofen- and acetaminophen-treated children in the observed risk of GI bleeding, acute renal failure, or anaphylaxis. No cases of Reye syndrome were seen in febrile children.

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

Post-Market Adverse Drug Reactions (Prescription Experience)

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

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

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

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

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

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

Allergic
Incidence less than 1%: anaphylaxis (See *Contraindications*).

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

Central Nervous System
Incidence 3 to 9%: dizziness.

Incidence 1 to 3%: headache, nervousness.

Incidence less than 1%: depression, insomnia.

Causal relationship unknown: paresthesias, hallucinations, dream abnormalities.

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

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

Incidence 1 to 3%: pruritus.

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

Causal relationship unknown: alopecia, Stevens-Johnson syndrome (symptoms include skin itch, rash and/or blisters).

Cardiovascular
Incidence less than 1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure.

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

Special Senses
Incidence 1 to 3%: tinnitus.

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

Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

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

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

Renal
Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia.

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

Hepatic
Incidence less than 1%: Hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin, and alkaline phosphatase).

Endocrine
Causal relationship unknown: gynecomastia, hypoglycaemic reaction.
Menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg t.i.d., for three days before menses.

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

Fluid retention generally responds promptly to drug discontinuation (See *Warnings and Precautions).*

DRUG INTERACTIONS

Serious Drug Interactions

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

Overview

Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu are not recommended for concomitant use with any other NSAIDs, including ASA. Documented or possible drug interactions with Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu include acetaminophen, digoxin, anticoagulants, oral antidiabetic agents and insulin, antihypertensives, diuretics, methotrexate, lithium and other protein-bound drugs.

Drug-Drug Interactions

Acetaminophen

Although interactions have not been reported, concurrent use with Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs
The use of Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu in addition to any other NSAID, including ASA, is not recommended due to the possibility of additive side effects. Animal studies show that aspirin given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been conducted.

No clinically meaningful loss of cardioprotection was found when patients on low-dose ASA (81 mg) were administered 400 mg ibuprofen T.I.D.[108]

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

Antacids[79]
A bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing aluminium hydroxide and magnesium hydroxide.

Antihypertensives
Prostaglandins are an important factor in cardiovascular homeostasis and inhibition of their synthesis by NSAIDs may interfere with circulatory control. NSAIDs may elevate blood pressure in patients receiving antihypertensive medication. Two meta analyses[72,73] have observed this relationship for NSAIDs as a class and for certain NSAIDs in particular, but ibuprofen did not significantly affect blood pressure in either meta analysis. Consistent with this lack of effect, a study by Davies et al[74] showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two -adrenergic blockers. Houston et al.[75] showed no effect of three weeks' therapy with ibuprofen on the antihypertensive efficacy of verapamil, but it is not known whether this lack of interaction extends to other classes of calcium channel blockers.

When renal perfusion pressure is reduced both prostaglandins and angiotensin II are important mediators of renal autoregulation.[76] As a class, the combination of an NSAID and angiotensin converting enzyme inhibitor theoretically may have the potential to decrease renal function. One study found a clinically significant decrease in renal function in 4 of 17 patients treated

with hydrochlorothioazide and fosinopril who received ibuprofen 2400 mg/day for one month.[77] In contrast, Minuz[78] found no effect on the antihypertensive effect of enalapril or on plasma renin or aldosterone following two days' treatment with ibuprofen 1200 mg/day.

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

Coumarin-type[70,71]
Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of ibuprofen with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary. Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. Nevertheless, the physician, should be cautious when administering Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops or Advil® Pediatric Drops Fever from Colds or Flu to patients on anticoagulants.

Digoxin[69]
Ibuprofen has been shown to increase serum digoxin concentration. Increased monitoring and dosage adjustments of digitalis glycoside may be necessary during and following concurrent ibuprofen therapy.

Diuretics
Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with ibuprofen, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

H-2 antagonists
In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

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

Lithium[81]
Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of

concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate[80]
Ibuprofen as well as other NSAIDs has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used when ibuprofen is administered concomitantly with methotrexate.

Selective Serotonin Reuptake Inhibitors (SSRIs)[109, 110]
Studies report an increased risk of gastrointestinal (GI) ulceration and bleeding when Ibuprofen as well as other NSAIDs are taken concomitantly with selective serotonin reuptake inhibitors (SSRIs) than when either class of drugs is taken alone (See Warnings and Precautions – Gastrointestinal).

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

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Do not take for fever for more than 3 days or for pain for more than 5 days unless directed by a physician.

The safety issues to consider when developing a dosage regimen of Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops, Advil® Pediatric Drops Fever from Colds or Flu for individual patients is applicable to:

- Elderly patients older than 65 years who are frail or debilitated and consideration should be

given to a starting dose lower than the one usually recommended (See *Warnings and Precautions*, *Elderly*).

Recommended Dose and Dosage Adjustment

Children under 12 years:

For all Advil® children's products, dose can be determined by using either child's age or weight. If possible, use weight to dose; otherwise use age.

CHILDREN'S ADVIL CHEWABLE TABLETS 50 mg/Tablet			
DIRECTIONS: DOSES BELOW MAY BE REPEATED EVERY 6-8 HOURS WHILE SYMPTOMS PERSIST, UP TO 4 DOSES A DAY, OR AS DIRECTED BY A PHYSICIAN.			
AGE	**WEIGHT**		**DOSE**
(yr)	**(kg)**	**(lbs)**	
Under 2	Under 10.9	Under 24	Recommend Advil Pediatric Drops
2-3	10.9 - 15.9	24 -35	2
4-5	16.0 - 21.3	36 - 47	3
6-8	21.4 - 26.7	48 - 59	4
9-10	26.8 - 32.5	60 - 71	5
11-12	32.6 - 43.0	72 - 95	6

CHILDREN'S ADVIL / CHILDREN'S ADVIL FEVER FROM COLDS OR FLU 20mg/ml (or 100mg/5ml)			
DIRECTIONS: SHAKE WELL BEFORE USE. DOSES BELOW MAY BE REPEATED EVERY 6-8 HOURS WHILE SYMPTOMS PERSIST, UP TO 3 DOSES A DAY, OR AS DIRECTED BY A PHYSICIAN.			
AGE	**WEIGHT**		**DOSE**
(yr)	**(kg)**	**(lbs)**	**(tsp)**
Under 2	Under 10.9	Under 24	5 mg/kg (0.25 mL/kg) To be calculated
2-3	10.9 - 15.9	24 -35	6.0 mL= 1 1/4 tsp
4-5	16.0 - 21.3	36 - 47	10 mL=2 tsp
6-8	21.4 - 26.7	48 - 59	12.5 mL = 2 ½ tsp
9-10	26.8 - 32.5	60 - 71	15 mL= 3 teaspoons
11-12	32.6 - 43.0	72 - 95	19.0 mL= 3 3/4 tsp

Note: Advil brand of ibuprofen is available for adults in tablet/caplet/capsule dosage/liquid gel forms. The equivalent adult dosage of Children's Advil or Children's Advil Fever from Colds or Flu (100 mg/5 mL) is 10 mL (2 teaspoons equivalent to 200 mg) taken every 4 hours or 20 mL (4 teaspoons equivalent to 400 mg) taken every 6 to 8 hours as needed. Do not to exceed 60 mL (12 teaspoons equivalent to 1200 mg) in 24 hours unless directed by a physician.

JUNIOR STRENGTH ADVIL / JUNIOR STRENGTH ADVIL FEVER FROM COLDS OR FLU 100 mg/Tablet			
DIRECTIONS: DOSES BELOW MAY BE REPEATED EVERY 6-8 HOURS WHILE SYMPTOMS PERSIST, UP TO 4 DOSES A DAY, OR AS DIRECTED BY A PHYSICIAN.			
AGE	**WEIGHT**		**DOSE**
(yr)	**(kg)**	**(lbs)**	
Under 2	Under 10.9	Under 24	Recommend Advil Pediatric Drops or Advil Pediatric Drops Fever from Colds or Flu
2-3	10.9 - 15.9	24 -35	1
4-5	16.0 - 21.3	36 - 47	1½
6-8	21.4 - 26.7	48 - 59	2
9-10	26.8 - 32.5	60 - 71	2½
11-12	32.6 - 43.0	72 - 95	3

Note: ADVIL brand of ibuprofen is available for adults in tablet/caplet/capsule/liquid gel dosage forms. The equivalent adult dosage of Junior Strength Advil or Junior Strength Advil Fever from Colds or Flu, (100 mg/tablet), is 2 tablets (200 mg) taken every 4 hours or 4 tablets (400 mg) taken every 6 to 8 hours as needed. Do not to exceed 12 tablets (1200 mg) in 24 hours unless directed by a physician.

ADVIL PEDIATRIC DROPS / ADVIL PEDIATRIC DROPS FEVER FROM COLDS OR FLU 40mg/ml (or 200mg/5ml)				
DIRECTIONS: SHAKE WELL BEFORE USE. USE ONLY WITH ENCLOSED ORAL SYRINGE. DOSES BELOW MAY BE REPEATED EVERY 6-8 HOURS WHILE SYMPTOMS PERSIST, UP TO 3 DOSES A DAY, OR AS DIRECTED BY A PHYSICIAN.				
Age	**Weight**		**Dosage**	
	(kg)	(lbs)		
0-3 months	2.5 - 5.4	5.5 - 11.9	5 mg/kg	To be calculated
4-11 months	5.5 - 7.9	12 - 17.5	5 mg/kg	1.0 ml
12-23 months	8.0 - 10.8	18 - 23	5 mg/kg	1.4 ml
2 - 3 years	10.9-15.9	24 - 35	10 mg/kg	3.0 ml

Missed Dose

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

Administration

See *Recommended Dose and Dosage Adjustment.*

OVERDOSAGE

Symptoms of Overdose[97-99]

The toxicity of ibuprofen overdose is dependent upon the amount of drug ingested and the time elapsed since ingestion; individual responses may vary, thus making it necessary to evaluate each

case separately. Although uncommon, serious toxicity and death have been reported with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other CNS symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, acute renal failure and apnoea (primarily in very young pediatric patients) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation, also have been reported.

Treatment of Overdose

In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption of ibuprofen when given less than 2 hours following ingestion. There is some evidence that repeated administration of activated charcoal may bind the medication that has diffused from the circulation.[109] Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. Management of hypotension, acidosis and gastrointestinal bleeding may be necessary.

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

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Examples of Ibuprofen Overdose

A 41-year-old man with multiple medical problems, including long-term renal insufficiency, developed near-fatal acute renal failure after ingestion of a massive dose (36 g) of ibuprofen [1]. He required dialysis for several months, at which point his renal function improved.

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

With electrolyte replacement and other intensive measures, a 21-month-old child recovered

within 5 days after accidental ingestion of 8 g of ibuprofen [2]. A 2-year-old child who ingested approximately 8 g of ibuprofen was treated with activated charcoal, developed metabolic acidosis and acute renal insufficiency, and recovered within 72 hours [3]. A 6-year-old child became comatose after ingesting 6 g of ibuprofen [4]. He was treated with gastric lavage, charcoal, and various supportive measures and recovered within 24 hours.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ibuprofen, like all nonsteroidal anti-inflammatory drugs (NSAIDs), is an analgesic, antipyretic, and anti-inflammatory medication.[1] There is strong evidence to support the view that the main mechanism of action of ibuprofen (like other NSAIDs) is related to decreasing prostaglandin biosynthesis.[2]

Prostaglandins are naturally-occurring fatty acid derivatives that are widely distributed in the tissues. They are believed to be a common factor in the production of pain, fever, and inflammation. Prostaglandins are believed to sensitise tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The enzyme catalysing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also known as cyclooxygenase. There is significant evidence that the main mechanism of analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition.[3] Other pharmacologic effects such as lysosome and plasma membrane stabilisation have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

A recent study confirmed that ibuprofen 400 mg provided a significantly faster onset of relief as measured by first perceptible relief, meaningful relief, per cent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache.[22]

Absorption: Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults.[4] Advil® Liqui-Gels contain solubilized ibuprofen which has peak serum concentrations within 36-42 minutes. In febrile children ages 3 months to < 12 years, the time of peak serum concentration was 1.60 and 1.54 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[5] Nahata[6] found a time to peak concentration of 1.1 and 1.2 hours for these respective doses. A similar study in febrile children by Walson[7] which used an ibuprofen suspension showed a time of peak serum concentration of 1.3 and 1.7 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively. Walson also found that mean ibuprofen plasma concentration at one hour was 21.7 6.7 and 28.4 15.2 g/mL for 5 mg/kg and 10 mg/kg, respectively. Food decreases the rate but not the extent of absorption.[4]

Distribution: The volume of distribution in adults after oral administration is 0.1-0.2 L/kg.[8] In febrile children the volume of distribution is 0.18 and 0.22 L/kg for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[5]

At therapeutic concentrations ibuprofen is highly bound to whole human plasma and to site II of purified albumin.[8] There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses.[4]

Ibuprofen excretion in breast milk following ingestion of one 400 mg ibuprofen tablet every 6 hours for five doses was below the level (i.e., 1μg/mL) of detection.[17] However, a later study using a more sensitive assay showed ibuprofen to be rapidly excreted in breast milk 30 minutes following oral ingestion of 400 mg of ibuprofen at a concentration of 13 ng/mL. A milk: plasma ratio of 1:126 was determined and the exposure of a suckling infant was calculated to be approximately 0.0008% of the maternal dose.[18] It is not known whether ibuprofen crosses the placenta.

Metabolism: Ibuprofen is a racemic mixture of R–(-) ibuprofen and S-(+) ibuprofen. R-(-) ibuprofen undergoes extensive enantiomeric conversion to S-(+) ibuprofen in humans, averaging between 53% and 65%.[9] S-(+) ibuprofen is believed to be the pharmacologically more active enantiomer. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl] propionic acid and 2-[4-(2-hydroxy-2-methylpropyl]propionic acid, have been identified in plasma and urine.[10] The metabolites 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been found in urine in very small concentrations.[11,12] Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen.[13] Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites.[8] Ibuprofen does not appear to induce the formation of drug metabolising enzymes in the rat.[10]

Excretion: Ibuprofen's plasma half-life in adults is 1.5-2.0 hours.[14] In febrile children the plasma half-life is 1.65 and 1.48 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively.[5] Parent drug and metabolites are primarily excreted in the urine; bile and faeces are relatively minor elimination routes. Total recovery in urine is between 70% and 90% of the administered dose within 24 hours.[8]

There is no evidence of a differential metabolism or elimination of ibuprofen in the elderly. A pharmacokinetic evaluation of ibuprofen in geriatric subjects (65 to 78 years) compared with young adult subjects (22 to 35 years) found that there was no clinically significant difference in the kinetic profiles of ibuprofen for these age groups.[15] Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites.

The pharmacokinetics of ibuprofen have also been evaluated in children, in whom the metabolism has been shown to be similar to that reported for adults. Walson reported that for ibuprofen 10 mg/kg given to children under 12 years of age, peak plasma concentration occurred at 1.5 hours and then declined with a plasma half-life of 1.8 hours.[16] Thus, ibuprofen appears to exhibit a similar pharmacokinetic profile in all age groups examined.

STORAGE AND STABILITY

Children's Advil®, Children's Advil® Fever from Colds or Flu, Children's Advil® Chewable Tablets, Junior Strength Advil®, Junior Strength Advil® Fever from Colds or Flu, Advil® Pediatric Drops and Advil® Pediatric Drops Fever from Colds or Flu should be stored in tightly-closed containers under room temperature (15-30°C) conditions.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

For Children:

Children's Advil® and Children's Advil® Fever from Colds or Flu:

Product name	Product Strengths	Product Appearance	Container size (commercial and/or professional sample)	Dosing Cup Size
Children's Advil®	100 mg/ 5 mL	Translucent blue, blue raspberry-flavoured, dye-free suspension	Polypropylene bottles of 100 mL and 230 mL	20 mL natural plastic molded dosage cup
		Translucent red, fruit-flavored suspension	Polypropylene bottles of 100 mL	
		Translucent purple, grape-flavoured suspension	Polypropylene bottles of 100 mL	
		White to off-white translucent, berry-flavoured, dye-free suspension	Polypropylene bottles of 100 mL	
		White to off-white, bubble gum-flavoured dye-free suspension	Polypropylene bottles of 100 mL, 120 mL and 230 mL	
		White to off-white, grape-flavoured dye-free suspension	Polypropylene bottles of 100 mL, 120 mL 230 mL and 260 mL	
		White to off-white translucent, berry-flavoured sugar free, dye-free suspension	Polypropylene bottles of 120 mL	
		White to off-white, grape-flavoured dye-free suspension	Polypropylene bottles of 25 mL (professional sample only)	20 mL natural plastic molded dosage cup

Product name	Product Strengths	Product Appearance	Container size (commercial and/or professional sample)	Dosing Cup Size
Children's Advil® Fever from Colds or Flu	100 mg/5 mL	White to off-white, grape-flavoured dye-free suspension	Polypropylene bottles of 100 mL	20 mL natural plastic molded dosage cup

Non-medicinal ingredients:

Blue Raspberry Flavour: Carboxymethylcellulose sodium, citric acid, disodium EDTA, FD&C Blue No. 1, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sodium citrate, sorbitol, sucrose, water, xanthan gum.

Dye-Free Berry Flavour: Carboxymethylcellulose sodium, citric acid, disodium EDTA, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sodium citrate, sorbitol, sucrose, water, xanthan gum.

Dye-Free Bubble Gum Flavour: Carboxymethylcellulose sodium, citric acid, disodium EDTA, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sorbitol, sucrose, water, xanthan gum.

Dye-Free Grape Flavour: Carboxymethylcellulose sodium, citric acid, disodium EDTA, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sorbitol, sucrose, water, xanthan gum.

Fruit Flavour: Carboxymethylcellulose sodium, citric acid, disodium EDTA, FD&C Red No.40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sorbitol, sucrose, water, xanthan gum.

Grape Flavour: Carboxymethylcellulose sodium, citric acid, disodium EDTA, FD&C Blue No. 1, FD&C Red No.40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sorbitol, sucrose, water, xanthan gum.

Sugar Free/Dye-Free Berry Flavour: Carboxymethylcellulose sodium, citric acid, disodium EDTA, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sodium citrate, sorbitol, sucralose, water, xanthan gum.

Junior Strength Advil® and Junior Strength Advil® Fever from Colds or Flu (Tablets): Fruit flavoured, ½" round, mottled red, flat-faced, beveled edged tablet with "Advil 100" debossed on one side and a bisect on the other; grape flavoured, ½" round mottled purple, flat-faced beveled edged tablet with "Advil 100" debossed on one side and a bisect on the other; and blue raspberry flavoured, ½" round, mottled blue, fat-faced, beveled edged tablet with "Advil 100" debossed on one side and a bisect on the other containing 100 mg ibuprofen are available in bottles of 20, 24, 40, 60and 2x40.

Non-Medicinal Ingredients:

Blue Raspberry Flavour: Aspartame (phenylalanine), cellulose acetate phthalate, FD&C Blue No. 1, FD&C Blue No. 2, flavour, gelatin, magnasweet, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide, sodium starch glycolate.

Fruit Flavour: Aspartame (phenylalanine), cellulose acetate phthalate, D&C Red No. 27, FD&C Red No. 40, flavour, gelatin, magnasweet, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide, sodium starch glycolate.

Grape Flavour: Aspartame (phenylalanine), cellulose acetate phthalate, D&C Red No. 30, FD&C Blue No. 2, flavour, gelatin, magnasweet, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide, sodium starch glycolate.

Dye-Free Grape Flavour: Aspartame (phenylalanine), cellulose acetate phthalate, flavour, gelatin, magnasweet, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide, sodium starch glycolate.

For Infants:

Advil® Pediatric Drops and Advil® Pediatric Drops Fever from Colds or Flu (Suspension): Translucent red, fruit-flavoured suspension, translucent purple, grape-flavoured suspension; and white to off-white, grape-flavoured dye-free suspension containing 40 mg ibuprofen per mL, is available in 15 mL and 24 mL bottles with an oral syringe.

Non-Medicinal Ingredients:

Dye-Free Grape Flavour: Citric acid, disodium EDTA, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sodium carboxymethylcellulose, sorbitol, sucrose, water, xanthan gum.

Fruit Flavour: Citric acid, disodium EDTA, FD&C Red No.40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sodium carboxymethylcellulose, sorbitol, sucrose, water, xanthan gum.

Grape Flavour: Citric acid, disodium EDTA, FD&C Blue No. 1, FD&C Red No.40, flavour, glycerin, microcrystalline cellulose, polysorbate 80, sodium benzoate, sodium carboxymethylcellulose, sorbitol, sucrose, water, xanthan gum.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

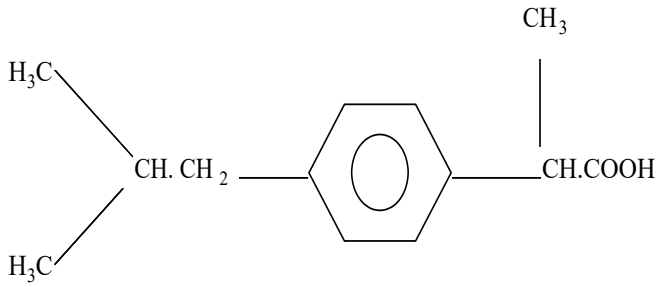
Proper name: Ibuprofen

Chemical name: α-methyl-4-(2-methylpropyl)benzeneacetic acid

Other names: p-isobutylhydratropic acid
2-(4-isobutylphenyl)-propionic acid

Molecular formula and molecular mass: $C_{13}H_{18}0_2$; 206.28

Structural formula:



Physicochemical properties: White or almost white powder or crystals with a characteristic odour.

Solubilities: Low solubility in water: soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether, and 1 in 1.5 of acetone. Ibuprofen is also soluble in an aqueous solution of alkali hydroxides and carbonates.

pKa and pH values: pH : 4.6 - 6.0, in a solution of 1 in 20.

Melting Point: 75 - 77˚C

CLINICAL TRIALS

Comparative Bioavailability Studies

Comparative Bioavailability: Advil® Liqui-Gels (fasted) and Children's Advil (fasted)

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

ADVIL® LIQUIGEL CAPSULES
(2 x 200 mg)
From Measured Data

Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	TEST	REFERENCE*	RATIO OF LEAST SQUARES MEANS***
AUC_T (μg·hr/mL)	135.17 138.05 (22.0%)	132.82 135.71 (22.7%)	99.3%
$AUC_{RefTmax}$ (μg·hr/mL)	13.1745 14.767 (49.3%)	16.5162 (18.138 (47.9%)	82.6%
AUC_I (μg·hr/mL)	136.52 139.63 (22.9%)	134.25 137.40 (23.8%)	99.2%
C_{max} (μg/mL)	47.33 47.6761 (12.1%)	42.47 42.8216 (13.2%)	111.1%
T_{max}** (h)	0.70 (35.2%)	0.81 (62.1%)	N /A
$T_{½}$** (h)	2.44 (16.2%)	2.53 (16.2%)	N/A

* Reference product: Pfizer Consumer Healthcare, a division of Pfizer Canada Inc. (20 mg/mL) Children's Advil® (ibuprofen) suspension, DIN 02232297.
** The T_{max} and $T_{½}$ parameters are expressed as the arithmetic means (CV%).
*** The ratio of least-squares means is reported in order to compensate for the unbalanced number subjects/sequence in this study.

A comparative, randomized, single-dose, 2-way crossover bioavailability study comparing ibuprofen 100 mg/5 mL (sugar free berry flavour) oral suspension (Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.) to Children's Advil® 100 mg/5 mL (fruit flavour) oral suspension (Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.) in 18 healthy adult male and female subjects under fasting conditions was conducted. The results of the study are summarized in the following table:

Ibuprofen (5 mL x 100 mg/5 mL) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (µg•h/mL)	30.99 31.61 (20)	31.53 32.14 (19)	98.30	95.33 – 101.37
AUC_I (µg•h/mL)	31.86 32.48 (20)	32.41 33.04 (19)	98.29	95.41 – 101.26
C_{max} (µg/mL)	9.767 9.93 (18)	9.993 10.11 (16)	97.74	89.71 – 106.48
T_{max}§ (h)	0.750 (0.50 – 3.00)	0.625 (0.50 – 2.00)		
$T_{½}$€ (h)	2.18 (22)	2.11 (22)		

*Ibuprofen 100 mg/5 mL (sugar free berry flavour) oral suspension (Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.).
†Children's Advil® 100 mg/5 mL (fruit flavour) oral suspension (Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.).
§Expressed as the median (range) only
€Expressed as the arithmetic mean (CV%) only

Published Literature

Fever

Multiple studies in the archival literature using ibuprofen doses ranging from 5 to 10 mg/kg have shown the drug's ability to lower fever in children, including fever due to colds and flu[7,39-59].

Pain

Several studies have been conducted to evaluate the efficacy of ibuprofen in mild to moderate pain arising from sore throat[60-62], otitis media[63,64], immunization[65], and post-surgery[66,67].

DETAILED PHARMACOLOGY

Animal Pharmacology

After single oral doses of 20 to 150 mg/kg of C^{14} labelled ibuprofen rats, the peak plasma level occurred at or before the earliest time examined (20 minutes in the 20 mg/kg group and 45 minutes in the 150 mg/kg group) and peak levels occurred with 45 minutes of dosing in nearly all tissues examined. The concentration in plasma and tissue decreased to very low levels by six hours after the 20 mg/kg dose and by 17 hours after the 150 mg/kg dose. Sixteen to 38% of the daily dose of ibuprofen was excreted in the urine.[100]

A similar dose was given to dogs for periods of up to six months with no evidence of accumulation of the drug or its metabolites.[100]

Inhibition of Platelet Aggregation in Animals

Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated by preventing platelet disposition in aortopulmonary arterial bypass grafts in the dog.[101] The drug's protective action against fatal pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to platelet inhibition.[102,103] Various prostaglandins and thromboxane A_2 (TXA_2), are important factors in normal platelet aggregation. Cyclooxygenase inhibition reduces TXA_2 production and release, thereby reducing platelet aggregation.[104] Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation,[105] but it is not known to what extent TXA_2 synthesis inhibition is involved in this effect.

Human Pharmacology

Two metabolites of ibuprofen were isolated from the urine of patients who had been treated for one month with the drug. The metabolites were identified at 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine.[100]

Effect of Ibuprofen on Platelet Aggregation, Bleeding and Clotting Times in Normal Volunteers

Platelet aggregation studies using the method of Sekhar were performed. Platelet aggregation fell significantly at a dosage of 1800 mg per day of 1buprofen when given over a period of 28 days.

Ibuprofen was also found to influence ADP induced aggregation to a lesser extent than that influenced by collagen. Platelet aggregation induced by recalcification of citrated platelet-rich plasma (a thrombin induced reaction) was not influenced by ibuprofen treatment. Likewise, ibuprofen did not affect whole blood clotting time on recalcification or prothrombin time. Bleeding time performed two hours after the administration of ibuprofen showed a significant dose related increase.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Single Dose Toxicity Studies

Single dose toxicity studies have been conducted using mice, rats, and dogs.[100]

The LD_{50} values for ibuprofen, expressed as mg/kg of body weight are as follows:

Mouse:	Oral	800 mg/kg
	Intraperitoneal	320 mg/kg
Rat:	Oral	1600 mg/kg
	Subcutaneous	1300 mg/kg

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.

Following single ibuprofen doses of 125 mg/kg and above to dogs effects were observed including emesis, transient albuminuria, faecal blood loss and erosions in the gastric antrum and pylorus; no ill effects were seen with 20 or 50 mg/kg doses.

Multiple Dose Studies

The no-effect level was determined using groups of 10 male and 10 female rats which were dosed orally for 26 weeks with 180, 60, 20 or 7.5 mg/kg ibuprofen in 0.4% hydroxyethyl cellulose. The control group consisted of 20 males and 20 females which received 0.4% hydroxyethyl cellulose. Rats were weighed three times daily and blood samples were obtained in the final week of dosing. The rats were sacrificed the day after the last dose and the internal organs examined.

Rats receiving ibuprofen for 26 weeks grew normally except for males on 180 mg/kg/day, which gained significantly less weight than the controls. One male rat receiving 180 mg/kg/day died due to intestinal lesions and the death was thought to be treatment-related. Both males and females receiving 180 mg/kg/day were anaemic; leukocyte count and plasma glutamic pyruvic transaminase activities were not significantly altered. The organ to body weight ratio of males given 180 mg/kg/day was typically greater than normal. For some organs, this was because the males weighed less than the controls. Organs that were enlarged were the liver, kidney, and spleen. The same organs were also enlarged in females receiving 180 mg/kg/day, although these females were similar in body weight to the controls. In addition, the combined seminal vesicle and prostate weight was subnormal and uterine weight was increased. The thyroid gland of males receiving 180, 60, 20 mg/kg/day exhibited a slight increase in weight, which was the same for the three doses, however no such increase was observed in the females. There were no significant histological changes observed in rat tissues except for the presence of intestinal ulcers in 1 male and 3 females receiving 180 mg/kg/day.

The above experiment was adapted to establish whether the effects of ibuprofen treatment on rats were reversible when dosing ended.[100] In this instance, rats were administered 180, 60, or 20 mg/kg/day ibuprofen for 13 weeks instead of 26 weeks, whereupon half the animals in each group were sacrificed and the remaining rats were maintained, undosed, for three weeks and then

sacrificed. Haematological examinations were performed after 4,8, and 12 weeks of treatment.

Results obtained from the dosing phase of this 13-week experiment reflected the results obtained previously, where rats were dosed for 26 weeks. Males receiving 180 mg/kg/day had enlarged kidneys, spleen, and testes; while those on lower doses had normal organ weights. Females on all three doses had enlarged kidneys, the extent of which was dose-dependent. Enlargement of the liver and ovaries was observed in females receiving 180 mg/kg/day, and of the spleen and ovaries on those on 60 mg/kg/day. None of the enlarged organs were histologically abnormal. Three weeks following withdrawal of treatment, the organ to body weight ratios had completely or almost completely returned to normal. Rats receiving 180 mg/kg/day were anaemic from week 4 of dosing and when examined after the final dose, were found to have intestinal lesions. These effects were not seen at the lower doses, thereby confirming the results of the first experiment. Since the highest dose of 180 mg/kg/day was only moderately toxic, an additional group of rats was dosed with 540 mg/kg/day.[102] All these rats died or were killed *in extremis* after 4 days' dosing. All had intestinal ulceration with peritonitis, and some also had slight renal tubular dilation.

The primary toxic effect of ibuprofen in rats is intestinal damage. Ibuprofen alters the organ to body weight ratio of certain organs, such as the liver, kidneys, gonads, and the secondary sex organs, although no histological abnormalities have occurred and the effect is reversible. The liver and kidney enlargement may be a reflection of work hypertrophy associated with the metabolism and excretion of the compound, whereas the significance of the effect on other organs is unknown. When administered in lethal doses, ibuprofen produces mild kidney lesions in addition to the intestinal damage.

Genotoxicity

Ibuprofen has shown no genotoxicity in the in vitro bacterial mutation assay in the presence and absence of S9 using *Salmonella* Typhimurium TA1535, TA1538, TA97a, TA100 and TA102.[112, 113] It was also tested in an in vivo sister chromatid exchange assay in the bone marrow cells of mice dosed orally or intraperitoneal and showed weak genotoxicity in the sister chromatid assay. There was no difference in the occurrence of chromosomal aberrations in cultured human lymphocytes in patients before or after treatment with ibuprofen.[114] A recent study in mouse bone marrow cells suggested a potential for chromosomal aberrations after oral dosing.[115] Overall, it was not genotoxic in vitro but was weakly mutagenic in vivo.

Carcinogenic Potential

Thirty male and 30 female rats were given 180 mg/kg/day of ibuprofen orally for 55 weeks and 60 mg/kg/day for the next 60 weeks. The only specific pathological effect observed was intestinal ulceration. There was no evidence of tumour induction and it is concluded that ibuprofen is not carcinogenic in the rat.[106]

Teratology Study in Rabbits

New Zealand white rabbits were given 0, 7.5, 20 and 60 mg/kg daily of ibuprofen from day 1 to day 29 of pregnancy. The mean foetal weight was unaffected; litter size was unaffected at the lower doses. Congenital malformations did occur in both treated and untreated groups with no consistent pattern except for one litter of 4 young with cylcopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.[100]

Teratology Study in Rats

Newly-mated female albino rats were given ibuprofen in doses of 0, 7.5, 20, 60 and 180 mg/kg/day from day 1 to day 20 of pregnancy; ibuprofen exhibited no embryotoxic or teratogenic effects even when administered at ulcerogenic doses.[100]

Penetration of Ibuprofen into the Rabbit and Rat Foetus

Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C^{14} labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and foetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and foetus indicating that the drug and its metabolites readily crossed the placental barrier into the foetal circulation.[100]

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PART III: CONSUMER INFORMATION

Children's Advil® Chewable Tablets
Ibuprofen Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when **Children's Advil Chewable Tablets** 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 Advil Chewable Tablets**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Provides up to 8 hours relief of fever. Fast and effective temporary relief of pain and fever due to colds or flu, sore throat, immunization, and earache.

What it does:
Ibuprofen reduces pain and fever.

Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which act by decreasing prostaglandin biosynthesis, which are natural occurring substances in the body involved in the production of pain and inflammation. Relief from pain may be expected in 0.5 hour.

When it should not be used:
Do not use Children's Advil Chewable Tablets if your child has or is:
- active or recurrent stomach ulcer or gastrointestinal bleeding, **or active inflammatory bowel disease (e.g. Crohn's, colitis)**
- taking acetylsalicylic acid (ASA), or any other NSAIDs including any other-ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, other NSAIDs or any of Children's Advil Chewable Tablets's ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have severe coronary artery disease,
- serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- right before or after heart surgery,
- excess potassium in the blood

or if you are in your third trimester of pregnancy.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
See outer product carton or composition section of product monograph.

What dosage forms it comes in:
Each tablet contains ibuprofen 50 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Children's Advil® Chewable Tablets talk to your doctor or pharmacist if:

- child has peptic ulcers, diabetes, high blood pressure, heart failure, heart or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, or is under doctor's care for any serious condition
- you are trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- you are taking any other drug including over the counter drugs.

Use with caution in the elderly.

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

Stop Use and Talk to a doctor if:
- Child does not get any relief within 24 hours.
- The symptoms such as pain or fever persist for more than 3 days.
- Redness or swelling is present in the painful area.
- Sore throat is severe, lasts for more than 2 days or occurs with fever or headache.

INTERACTIONS WITH THIS MEDICATION

Do not use this medicine if taking:
- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Talk to your doctor or pharmacist if you are taking other medication (prescription or non-prescription) such as any of the following (NOT a complete list):
acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics, cyclosporine, phenytoin, corticosteroids or benzodiazepines, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Doses below may be repeated every 6-8 hours while symptoms persist, up to 4 doses a day, or as directed by a doctor. If possible use weight to dose; otherwise use age. Do not use longer than 3 days for a fever or 5 days for pain relief.

Do not use more than the recommended amount.

Age	Weight		Dosage
(yrs.)	kg	lbs	
<2	Under 10.9	Under 24	**Use Advil Pediatric Drops**
2-3	10.9 - 15.9	24 -35	2
4-5	16.0 - 21.3	36 - 47	3
6-8	21.4 - 26.7	48 - 59	4
9- 10	26.8 - 32.5	60 - 71	5
11-12	32.6 - 43.0	72 - 95	6

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.
If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhoea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, fluid retention, itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other unexplained symptoms develop while taking Children's Advil® Chewable Tablets, discontinue use immediately and contact a doctor.

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Side effects may be minimized by using the smallest dose for the shortest duration of time.

This is not a complete list of side effects. For any unexpected effects while taking Children's Advil® Chewable Tablets, contact your doctor or pharmacist.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. This package has a child resistant cap. Do not use if body sleeve is broken or missing.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC, Mississauga, ON L5N 6L4 at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by
GlaxoSmithKline Consumer Healthcare ULC

Product monograph available to doctors and pharmacists upon request.

Last revised: March 12, 2021

PART III: CONSUMER INFORMATION

Children's Advil®
Ibuprofen Oral Suspension USP

This leaflet is part III of a three-part "Product Monograph" published when **Children's Advil** 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 Advil**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Provides up to 8 hours relief of fever. Fast and effective temporary relief of pain and fever due to colds or flu, sore throat, immunization, and earache.

What it does:
Ibuprofen reduces pain and fever.

Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which act by decreasing prostaglandin biosynthesis, which are natural occurring substances in the body involved in the production of pain and inflammation. Relief from pain may be expected in 0.5 hour.

When it should not be used:
Do not use Children's Advil®if your child has or is:
- active or recurrent stomach ulcer or gastrointestinal bleeding or active inflammatory bowel disease (e.g. Crohn's, colitis)
- taking acetylsalicylic acid (ASA), or NSAIDs including any other-ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, other NSAIDs or any of Children's Advil's ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have severe coronary artery disease,
- serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- if you are in your third trimester of pregnancy,
- right before or after heart surgery,
- excess potassium in the blood
- Or if you are in your third trimester of pregnancy.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
See outer product carton or composition section of product monograph.

What dosage forms it comes in:
Each 5 mL or 1 teaspoon of oral suspension contains ibuprofen 100 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Children's Advil talk to your doctor or pharmacist if:

- child has peptic ulcers, diabetes, high blood pressure, heart failure, heart or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, or is under doctor's care for any serious condition,
- you are trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- you are taking any other drug including over the counter drugs.

Use with caution in the elderly.

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

Stop Use and Talk to a doctor if:

- Child does not get any relief within 24 hours.
- The symptoms such as pain or fever persist for more than 3 days.
- Redness or swelling is present in the painful area.
- Sore throat is severe, lasts for more than 2 days or occurs with fever or headache.

INTERACTIONS WITH THIS MEDICATION

Do not use this medicine if you are taking:
- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Talk to your doctor or pharmacist if you are taking other medication (prescription or non-prescription) such as any of the following (NOT a complete list):
acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics cyclosporine, phenytoin, corticosteroids or benzodiazepines, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Shake well before using. Doses below may be repeated every 6-8 hours while symptoms persist, up to 3 doses a day, or as directed by a doctor. If possible use weight to dose; otherwise use age. Do not use longer than 3 days for a fever or 5 days for pain relief.

Do not use more than the recommended amount.

Age	Weight		Dosage
(yrs.)	kg	lbs	
<2	Under 10.9	Under 24	**Use Advil Pediatric Drops**
2-3	10.9 - 15.9	24 -35	1 ¼ teaspoons = 6 mL
4-5	16.0 - 21.3	36 - 47	2 teaspoons = 10 mL
6-8	21.4 - 26.7	48 - 59	2 ½ teaspoons = 12.5 mL
9- 10	26.8 - 32.5	60 - 71	3 teaspoons = 15 mL
11-12	32.6 - 43.0	72 - 95	3 3/4 teaspoons =19 mL

Advil brand of ibuprofen is available for adults in tablet/caplet/capsule/liquid gel dosage forms. The equivalent adult dosage of Children's Advil (100 mg/5 mL) is 10 mL (2 teaspoons equivalent to 200 mg) taken every 4 hours or 20 mL (4 teaspoons equivalent to 400 mg) taken every 6 to 8 hours as needed. Do not to exceed 60 mL (12 teaspoons equivalent to 1200 mg) in 24 hours unless directed by a physician."Use the lowest effective dose for the shortest duration.

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.
If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhoea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, fluid retention, itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other unexplained symptoms develop while taking Children's Advil, discontinue use immediately and contact a doctor.

Side effects may be minimized by using the smallest dose for the shortest duration of time.

This is not a complete list of side effects. For any unexpected effects while taking Children's Advil, contact your doctor or pharmacist.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. This package has a child resistant cap. Do not use if body sleeve is broken or missing.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC, Mississauga, ON L5N 6L4 at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by
GlaxoSmithKline Consumer Healthcare ULC

Product monograph available to doctors and pharmacists upon request.
Last revised: March 12, 2021

PART III: CONSUMER INFORMATION

Junior Strength Advil®
Ibuprofen Tablets USP

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

ABOUT THIS MEDICATION

What the medication is used for:
Provides up to 8 hours relief of fever. Fast and effective temporary relief of pain and fever due to colds or flu, sore throat, immunization, and earache.

What it does:
Ibuprofen reduces pain and fever.

Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which act by decreasing prostaglandin biosynthesis, which are natural occurring substances in the body involved in the production of pain and inflammation. Relief from pain may be expected in 0.5 hour.

When it should not be used:
Do not use Junior Strength Advil if your child has or is:
- active or recurrent stomach ulcer or gastrointestinal bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis)
- taking acetylsalicylic acid (ASA), or any other NSAIDs including any other-ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, other NSAIDs or any of Junior Strength Advil's ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have severe coronary artery disease,
- serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- right before or after heart surgery,
- excess potassium in the blood,
- or if you are in your third trimester of pregnancy.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
See outer product carton or composition section of product monograph.

What dosage forms it comes in:
Each tablet contains ibuprofen 100 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Junior Strength Advil® talk to your doctor or pharmacist if:

- child has peptic ulcers, diabetes, high blood pressure, heart failure, heart or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, or is under doctor's care for any serious condition
- you are trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- you are taking any other drug including over the counter drugs.

Use with caution in the elderly.

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

Stop Use and Talk to a doctor if:

- Child does not get any relief within 24 hours.
- The symptoms such as pain or fever persist for more than 3 days.
- Redness or swelling is present in the painful area.
- Sore throat is severe, lasts for more than 2 days or occurs with fever or headache.

INTERACTIONS WITH THIS MEDICATION

Do not use this medicine if taking:
- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Talk to your doctor or pharmacist if you are taking other

medication (prescription or non-prescription) such as any of the following (NOT a complete list):
acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics cyclosporine, phenytoin, corticosteroids or benzodiazepines, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Doses below may be repeated every 6-8 hours while symptoms persist, up to 4 doses a day, or as directed by a doctor. If possible use weight to dose; otherwise use age. Do not use longer than 3 days for a fever or 5 days for pain relief.

Do not use more than the recommended amount.

Age	Weight		Dosage
(yrs.)	kg	lbs	
<2	Under 10.9	Under 24	**Use Advil Pediatric Drops**
2-3	10.9 - 15.9	24 -35	1
4-5	16.0 - 21.3	36 - 47	1½
6-8	21.4 - 26.7	48 - 59	2
9- 10	26.8 - 32.5	60 - 71	2½
11-12	32.6 - 43.0	72 - 95	3

ADVIL brand of ibuprofen is available for adults in tablet/caplet/capsule/liquid gel dosage forms. The equivalent adult dosage of Junior Strength Advil, (100 mg/tablet), is 2 tablets (200 mg) taken every 4 hours or 4 tablets (400 mg) taken every 6 to 8 hours as needed. Do not to exceed 12 tablets (1200 mg) in 24 hours unless directed by a physician.Use the lowest effective dose for the shortest duration.

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.
If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhoea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, fluid retention, itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other unexplained symptoms develop while taking Junior Strength Advil, discontinue use immediately and contact a doctor.

Side effects may be minimized by using the smallest dose for the shortest duration of time.

This is not a complete list of side effects. For any unexpected effects while taking Junior Strength Advil®, contact your doctor or pharmacist.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. This package has a child resistant cap. Do not use if body sleeve is broken or missing.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC, Mississauga, ON L5N 6L4 at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by
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Product monograph available to doctors and pharmacists upon request.
Last revised: March 12, 2021

PART III: CONSUMER INFORMATION

Advil Pediatric Drops
Ibuprofen Oral Suspension USP

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

ABOUT THIS MEDICATION

What the medication is used for:
Provides up to 8 hours relief of fever. Fast and effective temporary relief of pain and fever due to colds, sore throat, immunization, and earache.

What it does:
Ibuprofen reduces pain and fever.

Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which act by decreasing prostaglandin biosynthesis, which are natural occurring substances in the body involved in the production of pain and inflammation. Relief from pain may be expected in 0.5 hour.

When it should not be used:
Do not use Advil Pediatric Drops if your child has or is:
- active or recurrent stomach ulcer or gastrointestinal bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis)
- taking acetylsalicylic acid (ASA), or any other NSAIDs including any other ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, other NSAIDs, or any of Advil Pediatric Drops ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have severe coronary artery disease,
- serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- right before or after heart surgery,
- excess potassium in the blood
- or if you are in your third trimester of pregnancy.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
See outer product carton or composition section of product monograph.

What dosage forms it comes in:
Each mL of oral suspension contains ibuprofen 40 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Advil Pediatric Drops talk to your doctor or pharmacist if:

- Child has peptic ulcers, diabetes, high blood pressure, heart failure heart or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, or is under doctor's care for any serious condition
- you are trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- you are taking any other drug including over the counter drugs.

Use with caution in the elderly.

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

Stop Use and Talk to a doctor if:

- Child does not get any relief within 24 hours.
- The symptoms such as pain or fever persist for more than 3 days.
- Redness or swelling is present in the painful area.
- Sore throat is severe, lasts for more than 2 days or occurs with fever or headache.

INTERACTIONS WITH THIS MEDICATION

Do not use this medicine if taking:
- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the

preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Talk to your doctor or pharmacist if you are taking other medication (prescription or non-prescription) such as any of the following (NOT a complete list):
acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics cyclosporine, phenytoin, corticosteroids or benzodiazepines, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Shake well before using. Use only with enclosed oral syringe. Doses below may be repeated every 6-8 hours while symptoms persist, up to 3 doses a day, or as directed by a doctor. If possible use weight to dose; otherwise use age. Do not use longer than 3 days for a fever or 5 days for pain relief.

Do not use more than the recommended amount.

Age	Weight		Dosage
	(kg)	(lbs)	
0-3 months	2.5-5.4	5.5-11.9	talk to a doctor
4-11 months	5.5-7.9	12-17.5	1 ml
12-23 months	8.0-10.8	18-23	1.4 ml
2-3 years	10.9-15.9	24-35	3 ml

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.
If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhoea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, fluid retention, itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other unexplained symptoms develop while taking Advil Pediatric Drops, discontinue use immediately and contact a doctor.

Side effects may be minimized by using the smallest dose for the shortest duration of time.

This is not a complete list of side effects. For any unexpected effects while taking Advil® Pediatric Drops, contact your doctor or pharmacist.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. This package has a child resistant cap. Do not use if body sleeve is broken or missing.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC
, Mississauga, ON L5N 6L4 at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by
GlaxoSmithKline Consumer Healthcare ULC

Product monograph available to doctors and pharmacists upon request.

Last revised: March 12, 2021

PART III: CONSUMER INFORMATION

Children's Advil® Fever from Colds or Flu
Ibuprofen Oral Suspension USP

This leaflet is part III of a three-part "Product Monograph" published when **Children's Advil Fever from Colds or Flu** 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 Advil Fever from Colds or Flu.** Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Provides up to 8 hours relief of fever. Fast and effective temporary relief of pain and fever due to colds or flu, sore throat, immunization, and earache.

What it does:
Ibuprofen reduces pain and fever.

Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which act by decreasing prostaglandin biosynthesis, which are natural occurring substances in the body involved in the production of pain and inflammation. Relief from pain may be expected in 0.5 hour.

When it should not be used:
Do not use Children's Advil Fever from Colds or Flu if your child has or is:

- active or recurrent stomach ulcer or gastrointestinal bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis)
- taking acetylsalicylic acid (ASA), or any other NSAIDs including any other ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, ~~or~~ other NSAIDs, or any of Children's Advil Fever from Colds or Flu's ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), uticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have severe coronary artery disease,
- serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- right before or after heart surgery,
- excess potassium in the blood
- or if you are in your third trimester of pregnancy.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
See outer product carton or composition section of product monograph.

What dosage forms it comes in:
Each 5 mL or 1 teaspoon of oral suspension contains ibuprofen 100 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Children's Advil Fever from Colds or Flu talk to your doctor or pharmacist if:

- child has peptic ulcers, diabetes, high blood pressure, heart failure, heart or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, or is under doctor's care for any serious condition
- you are trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- you are taking any other drug including over the counter drugs.

Use with caution in the elderly

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

Stop Use and Talk to a doctor if:

- Child does not get any relief within 24 hours.
- The symptoms such as pain or fever persist for more than 3 days.
- Redness or swelling is present in the painful area.
- Sore throat is severe, lasts for more than 2 days or occurs with fever or headache.

INTERACTIONS WITH THIS MEDICATION

Do not use this medicine if you are taking:

- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.

- ASA or other anti-inflammatory medication.

Talk to your doctor or pharmacist if you are taking other medication (prescription or non-prescription) such as any of the following (NOT a complete list):
: acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics,cyclosporine, phenytoin, corticosteroids or benzodiazepines, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Shake well before using. Use only with measuring device provided. Doses below may be repeated every 6-8 hours while symptoms persist, up to 3 doses a day, or as directed by a doctor. If possible use weight to dose; otherwise use age. Do not use longer than 3 days for a fever or 5 days for pain relief.

Do not use more than the recommended amount. .

Age	Weight		Dosage
(yrs.)	kg	lbs	
<2	Under 10.9	Under 24	**Use Advil Pediatric Drops**
2-3	10.9 - 15.9	24 -35	1 ¼ teaspoons = 6 mL
4-5	16.0 - 21.3	36 - 47	2 teaspoons = 10 mL
6-8	21.4 - 26.7	48 - 59	2 ½ teaspoons = 12.5 mL
9- 10	26.8 - 32.5	60 - 71	3 teaspoons = 15 mL
11-12	32.6 - 43.0	72 - 95	3 3/4 teaspoons =19 mL

Advil brand of ibuprofen is available for adults in tablet/caplet/capsule/liquid gel dosage forms. The equivalent adult dosage of Children's Advil Fever from Colds or Flu (100 mg/5 mL) is 10 mL (2 teaspoons equivalent to 200 mg) taken every 4 hours or 20 mL (4 teaspoons equivalent to 400 mg) taken every 6 to 8 hours as needed. Do not to exceed 60 mL (12 teaspoons equivalent to 1200 mg) in 24 hours unless directed by a physician.Use the lowest effective dose for the shortest duration

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.

If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhoea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, fluid retention, itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other unexplained symptoms develop while taking Children's Advil Fever from Colds or Flu**,** discontinue use immediately and contact a doctor.

Side effects may be minimized by using the smallest dose for the shortest duration of time.

This is not a complete list of side effects. For any unexpected effects while taking Children's Advil® Fever from Colds or Flu, contact your doctor or pharmacist.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. This package has a child resistant cap. Do not use if body sleeve is broken or missing.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC, Mississauga, ON L5N 6L4 at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by
GlaxoSmithKline Consumer Healthcare ULC.
Product monograph available to doctors and pharmacists upon request.

Last revised: March 12, 2021

PART III: CONSUMER INFORMATION

Junior Strength Advil® Fever from Colds or Flu
Ibuprofen Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when **Junior Strength Advil Fever from Colds or Flu** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Junior Strength Advil Fever from Colds or Flu**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Provides up to 8 hours relief of fever. Fast and effective temporary relief of pain and fever due to colds or flu, sore throat, immunization, and earache.

What it does:
Ibuprofen reduces pain and fever.

Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which act by decreasing prostaglandin biosynthesis, which are natural occurring substances in the body involved in the production of pain and inflammation. Relief from pain may be expected in 0.5 hour.

When it should not be used:
Do not use Junior Strength Advil Fever from Colds or Flu if your child has or is:

- active or recurrent stomach ulcer or gastrointestinal bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis)
- taking acetylsalicylic acid (ASA), or any other NSAIDs including any other ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, other non-steroidal anti-inflammatory drugs (NSAIDs), or any of Junior Strength Advil Fever from Colds or Flu's ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have severe coronary artery disease,
- serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- right before or after heart surgery,
- excess potassium in the blood
- or if you are in your third trimester of pregnancy.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
See outer product carton or composition section of product monograph.

What dosage forms it comes in:
Each tablet contains ibuprofen 100 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Junior Strength Advil Fever from Colds or Flu talk to your doctor or pharmacist if:

- child has peptic ulcers, diabetes, high blood pressure, heart failure, heart or thyroid disease, asthma, kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, or is under doctor's care for any serious condition
- you are trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- you are taking any other drug including over the counter drugs.

Use with caution in the elderly

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

Stop Use and Talk to a doctor if:

- Child does not get any relief within 24 hours.
- The symptoms such as pain or fever persist for more than 3 days.
- Redness or swelling is present in the painful area.
- Sore throat is severe, lasts for more than 2 days or occurs with fever or headache.

INTERACTIONS WITH THIS MEDICATION

Do not use this medicine if you are taking:

- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Talk to your doctor or pharmacist if you are taking other medication (prescription or non-prescription) such as any of the following (NOT a complete list):
acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics,cyclosporine, phenytoin, corticosteroids or benzodiazepines, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Doses below may be repeated every 6-8 hours while symptoms persist, up to 4 doses a day, or as directed by a doctor. If possible use weight to dose; otherwise use age. Do not use longer than 3 days for a fever or 5 days for pain relief.

Do not use more than the recommended amount. .

Age	Weight		Dosage
(yrs.)	kg	lbs	
<2	Under 10.9	Under 24	**Use Advil Pediatric Drops**
2-3	10.9 - 15.9	24 -35	1
4-5	16.0 - 21.3	36 - 47	1½
6-8	21.4 - 26.7	48 - 59	2
9- 10	26.8 - 32.5	60 - 71	2½
11-12	32.6 - 43.0	72 - 95	3

ADVIL brand of ibuprofen is available for adults in tablet/caplet/capsule dosage forms. The equivalent adult dosage of Junior Strength Advil Fever from Colds or Flu, (100 mg/tablet), is 2 tablets (200 mg) taken every 4 hours or 4 tablets (400 mg) taken every 6 to 8 hours as needed. Do not to exceed 12 tablets (1200 mg) in 24 hours unless directed by a physician.Use the lowest effective dose for the shortest duration.

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.
If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhoea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, fluid retention, itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other unexplained symptoms develop while taking Junior Strength Advil Fever from Colds or Flu**,** discontinue use immediately and contact a doctor.

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Side effects may be minimized by using the smallest dose for the shortest duration of time.

This is not a complete list of side effects. For any unexpected effects while taking Junior Strength Advil® Fever from Colds or Flu, contact your doctor or pharmacist.

REPORTING SUSPECTED 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. This package has a child resistant cap. Do not use if body sleeve is broken or missing.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC
, Mississauga, ON L5N 6L4 at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by
GlaxoSmithKline Consumer Healthcare ULC

Product monograph available to doctors and pharmacists upon request.

Last revised: March 12, 2021

PART III: CONSUMER INFORMATION

Advil Pediatric Drops Fever from Colds or Flu
Ibuprofen Oral Suspension USP

This leaflet is part III of a three-part "Product Monograph" published when **Advil Pediatric Drops Fever from Colds or Flu** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Advil Pediatric Drops Fever from Colds or Flu**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Provides up to 8 hours relief of fever. Fast and effective temporary relief of pain due to colds, sore throat, immunization and earache.

What it does:
Ibuprofen reduces pain and fever.

Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), which act by decreasing prostaglandin biosynthesis, which are natural occurring substances in the body involved in the production of pain and inflammation. Relief from pain may be expected in 0.5 hour.

When it should not be used:
Do not use Advil® Pediatric Drops Fever from Colds or Flu if your child has or is:
- active or recurrent stomach ulcer or gastrointestinal bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis)
- taking acetylsalicylic acid (ASA), or any other NSAIDs, including any other ibuprofen product,
- allergic/hypersensitive to ASA, ibuprofen, other salicylates, other NSAIDs, or any of Advil Pediatric Drops Fever from Colds or Flu's ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), uticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have severe coronary artery disease,
  serious liver or kidney disease,
- Systemic Lupus Erythematosus,
- right before or after heart surgery,
- excess potassium in the blood
- or if you are in your third trimester of pregnancy.

What the medicinal ingredient is:
Ibuprofen.

What the important nonmedicinal ingredients are:
See outer product carton or composition section of product monograph.

What dosage forms it comes in:
Each mL of oral suspension contains ibuprofen 40 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer. The chance of stomach bleeding is higher if you are: age 60 or older, have had stomach ulcers or bleeding problems, take a blood thinner or steroid drug, take with other drugs containing an NSAID like ASA, ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.

BEFORE you use Advil Pediatric Drops Fever from Colds or Flu talk to your doctor or pharmacist if:
- child has peptic ulcers, diabetes, high blood pressure, heart failure heart or thyroid disease, asthma-kidney or liver disease, glaucoma, blood clotting disorder (such as hemophilia), any other serious disease, or is under doctor's care for any serious condition
- you are trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- you are taking any other drug including over the counter drugs.

Use with caution in the elderly.

Long-term continuous use may increase the risk of heart attack or stroke.
Stop Use and Talk to a doctor if:

- Child does not get any relief within 24 hours.
- The symptoms such as pain or fever persist for more than 3 days.
- Redness or swelling is present in the painful area.
- Sore throat is severe, lasts for more than 2 days or occurs with fever or headache.

INTERACTIONS WITH THIS MEDICATION

Do not use this medicine if taking:
- Daily low dose ASA (81 – 325 mg), without talking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Talk to your doctor or pharmacist if you are taking other medication (prescription or non-prescription) such as any of the

following (NOT a complete list):
acetaminophen, anticoagulants (blood thinners), digoxin, oral antidiabetic agents and insulin, diuretics, methotrexate, lithium, protein-bound drugs including probenecid, thyroxine, antibiotics, cyclosporine, phenytoin, corticosteroids or benzodiazepines, other NSAIDs, or medications for high blood pressure. Tell your doctor or pharmacist what prescription drugs you are taking or plan to take.

PROPER USE OF THIS MEDICATION

Usual dose:
Shake well before using. Use only with enclosed oral syringe. Doses below may be repeated every 6-8 hours while symptoms persist, up to 3 doses a day, or as directed by a doctor. If possible use weight to dose; otherwise use age. Do not use longer than 3 days for a fever or 5 days for pain relief.

Do not use more than the recommended amount.

Age	Weight		Dosage
	(kg)	(lbs)	
0-3 months	2.5-5.4	5.5-11.9	talk to a doctor
4-11 months	5.5-7.9	12-17.5	1 ml
12-23 months	8.0-10.8	18-23	1.4 ml
2-3 years	10.9-15.9	24-35	3 ml

Overdose:

In case of overdose, call a Poison Control Centre or a doctor immediately, even if there are no symptoms.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.
If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhoea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness or any change in vision, fluid retention, itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, or any other unexplained symptoms develop while taking Advil Pediatric Drops Fever from Colds or Flu, discontinue use immediately and contact a doctor.

Side effects may be minimized by using the smallest dose for the shortest duration of time.

This is not a complete list of side effects. For any unexpected effects while taking Advil® Pediatric Drops Fever from Colds or Flu, contact your doctor or pharmacist.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep out of reach of children. This package contains enough medicine to seriously harm a child. This package has a child resistant cap. Do not use if body sleeve is broken or missing.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare ULC
, Mississauga, ON L5N 6L4 at: 1-888-275-9938 or www.advil.ca.

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