PRODUCT MONOGRAPH

Children's MOTRIN® Cold

ibuprofen and pseudoephedrine hydrochloride oral suspension

100 mg/5 mL ibuprofen and
15 mg/5 mL pseudoephedrine hydrochloride

Analgesic/Antipyretic and
Decongestant

McNeil Consumer Healthcare,
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	100mg/5 mL ibuprofen and 15 mg/5 mL pseudoephedrine hydrochloride oral suspension	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Children's MOTRIN® Cold (ibuprofen and pseudoephedrine hydrochloride) is indicated for:

- effective relief of symptoms associated with the common cold, flu, or sinusitis, including nasal and sinus congestion, stuffy nose, headache, sore throat, body aches and pains, and for the temporary reduction of fever in pediatric patients aged 4 to 11 years of age.

CONTRAINDICATIONS

- Children's MOTRIN® Cold should not be used in patients:

- who are hypersensitive to ibuprofen, pseudoephedrine hydrochloride, other non-steroidal anti-inflammatory drugs, or to any ingredient in the formulation. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph. The potential for cross-reactivity between different NSAIDs must be kept in mind.

- with kidney disease and or who have suffered significant fluid loss.

- with the complete or partial syndrome of acetylsalicylic acid (ASA) intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are

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

- with active gastric or duodenal ulcer, a history of recurrent ulceration, or active inflammatory disease of the gastrointestinal system.

- with significant hepatic impairment or active liver disease.

- severely impaired or deteriorating renal function (creatinine clearance <30 ml/min).

- Ibuprofen should not be used in the presence of known hyperkalemia (also see Warnings and Precautions – Renal section).

- Children with kidney disease and/or who have suffered significant fluid loss.

- Children's MOTRIN® Cold should not be used during pregnancy because its safety under this condition has not been established. Ibuprofen levels in breast milk are extremely low and are unlikely to affect a nursing infant, however because its safety under these conditions has not been established, consult a physician before use in nursing mothers.

- Children's MOTRIN® Cold should not be used in patients with hypertension, coronary artery disease and in patients on monoamine oxidase inhibitor (MAOI) therapy.

- Ibuprofen is contraindicated in patients with Systemic Lupus Erythematosus as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been previously administered. Aseptic meningitis has also been reported.

WARNINGS AND PRECAUTIONS

Although this product is intended for a pediatric population, ibuprofen and pseudoephedrine should be used only under the supervision of a physician in patients with the following conditions:

- Patients with heart disease, high blood pressure, thyroid disease, narrow angle glaucoma or difficulty in urination due to enlargement of the prostate gland should not take this drug unless directed by a physician (see Warnings and Precautions – General).

- Caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (see Warnings and Precautions – Cardiovascular and Drug Interactions – Anti-hypertensives).

- Caution in 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 (see Warnings and Precautions – Gastrointestinal and Drug Interactions).

- 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 persistent urinary symptoms (bladder pain, dysuria, urinary frequency), 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).

General

Several medical conditions which can predispose patients to the adverse effects of non-steroidal anti-inflammatory drugs in general may be applicable to ibuprofen.

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

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

Long-term ingestion of combinations of analgesics has been associated with the condition analgesic nephropathy. It is therefore appropriate that patients be discouraged from long-term unsupervised consumption of analgesics, particularly in combination. Patients should be directed to consult a physician if their underlying condition requires administration of Children's MOTRIN® Cold for more than 5 days. Children's MOTRIN® Cold usually should not be administered along with acetaminophen or acetylsalicylic acid.

Patients with any serious medical condition should consult a physician before using Children's MOTRIN® Cold. There is a possibility of insomnia, if this medicine is taken before bedtime.

Carcinogenesis and Mutagenesis

See Toxicology Section.

Cardiovascular
Some patients with pre-existing hypertension may develop worsening of blood pressure control when placed on an NSAID and regular monitoring of blood pressure should be performed under such circumstances. NSAIDs may exacerbate congestive heart failure.

Patients who are taking low-dose ASA as cardio protective therapy should consult with a health professional prior to taking ibuprofen (see also Drug Interactions - Acetylsalicylic Acid). Patients with high blood pressure or heart disease should take Children's MOTRIN® Cold only under the advice and supervision of a physician. Conditions such as congestive heart failure and hypertension may be aggravated by sodium retention and edema caused by ibuprofen in such patients.

Dependence/Tolerance
Not applicable.

Ear/Nose/Throat
Not applicable.

Endocrine and Metabolism
Patients with thyroid disease should take Children's MOTRIN® Cold only under the advice and supervision of a physician.

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

Gastrointestinal
Serious GI toxicity, such as ulceration, perforation, obstruction and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen.

GI symptoms, such as dyspepsia, are common, usually developing early in therapy. Health providers 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 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. The incidence of these complications is related to dose, past history of known ulcer disease, and advanced age (see Special Populations). Studies have shown that the use of oral corticosteroids increases the risk of upper gastrointestinal complications associated with NSAIDs.

Ibuprofen should be given under close medical supervision to patients with a history of ulcer of the upper gastrointestinal tract or inflammatory disease of the gastrointestinal tract such as

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

Health providers should inform patients about the signs and symptoms of serious GI toxicity and instruct them to contact a health provider 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, health providers should follow chronically treated patients and watch for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs ibuprofen 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 *Helicobacter pylori* infection, excess alcohol intake, smoking, and concomitant oral steroids, anti-coagulants, anti-platelet agents (including ASA), or selective serotonin reuptake inhibitors (SSRIs).

The administration of ibuprofen with food or milk is recommended since occasional and mild heartburn, upset stomach or stomach pain may occur with its use. Patients should be advised to seek the consultation of a physician if gastrointestinal side effects occur consistently, persist, or appear to worsen.

Patients taking ibuprofen should be cautioned to report to their physician signs or symptoms of GI intolerance and/or bleeding.

Patients taking oral corticosteroids should consult with a health professional before taking ibuprofen. Studies have shown that the use of oral corticosteroids increases the risk of upper gastrointestinal complications associated with NSAIDs.

Genitourinary

Some NSAIDs are associated with 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. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with ibuprofen should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are considered.

Hematologic

Children's MOTRIN® Cold, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less than that seen with acetylsalicylic acid. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying

haemostatic defects, Children's MOTRIN® Cold should be avoided by persons with intrinsic coagulation defects and by those on anticoagulant therapy.

Hepatic/Biliary/Pancreatic

Patients with diabetes should take Children's MOTRIN® Cold only under the advice and supervision of a physician.

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

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with nonsteroidal anti-inflammatory drugs.

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

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

Immune

Anaphylactoid reactions have occurred after administration of ibuprofen to patients with known acetylsalicylic acid or other NSAID sensitivity manifested as asthma, swelling, shock or hives. Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

As with NSAIDs in general, some patients may experience urticaria and angioedema upon exposure to ibuprofen. Ibuprofen should not be given to patients with the complete or partial syndrome of ASA-intolerance (see Contraindications).

Neurologic

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

In occasional rare 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 tissues diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health provider must be vigilant to the development of this complication.

Ophthalmologic
Blurred and/or diminished vision, scotoma, and/or changes in colour vision have been reported. If a patient develops such complaints while taking Children's MOTRIN® Cold, the drug should be discontinued. Patients with any visual disturbances should have an ophthalmologic examination.

Peri-Operative Considerations
In general, NSAIDS should be discontinued prior to surgeries to decrease the risk of post-operative bleeding.

Psychiatric
Not applicable.

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

Long-term ingestion of combinations of analgesics has been associated with the condition analgesic nephropathy. It is therefore appropriate that patients be discouraged from long-term unsupervised consumption of analgesics, particularly in combination. Patients should therefore be directed to consult a physician if their underlying condition requires administration of Children's MOTRIN® Cold for more than 5 days. Children's MOTRIN® Cold usually should not be administered along with acetaminophen or acetylsalicylic acid.

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

Mild impairment of renal function (decreased renal blood flow and glomerular filtration rate) can occur at maximal doses of ibuprofen. Renal papillary necrosis has been reported.

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

A second form of renal toxicity has been seen in patients with pre-renal conditions leading to 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 non-steroidal 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 (Glomerular Filtration Rate (GFR) < 60 ml/min or 1 ml/sec), patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, those taking diuretics, angiotensin-converting enzyme inhibitors, angiotensin-II receptor

blockers, cyclosporin, ASA and the elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short-term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate an NSAID under stable conditions may decompensate during periods of added stress, for example during states of fluid restriction as can occur during gastroenteritis. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

NSAIDs can increase the risk of hyperkalemia. In patients on dialysis, NSAIDs should be used with caution.

Fluid retention and edema have been observed in patients treated with ibuprofen. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Ibuprofen should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention. Ask patients who are on chronic therapy and at risk for fluid retention to weigh themselves at regular intervals to assist in monitoring for fluid accumulation.

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 angiotensin-II receptor antagonists, adrenergic blockers, angiotensin-converting enzyme inhibitors or some diuretics. Patients at risk should be monitored periodically during long-term therapy.

Pseudoephedrine and its active metabolite are excreted chiefly via the kidneys. Therefore, dosage should be adjusted in patients with impaired kidney function. Myoclonic jerking and bizarre behaviour were reported in a haemodialysis patient with end-stage renal failure after taking 60mg of pseudoephedrine four times daily for 12 days to treat nasal congestion.

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
Not applicable.

Sexual Function/Reproduction
Not applicable.

Skin
In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis 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~~ signs or symptoms or skin rash or edema they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Pseudoephedrine may induce non-pigmenting, fixed-type skin eruptions, which are typically indurated, erythematous, pruritic, tender and oedematous. The reaction tends to occur within 24 hours after administration of pseudoephedrine and to resolve 2 to 3 days after discontinuation.

Special Populations

Pregnant Women:
No evidence specifically identifies exposure to analgesic doses of ibuprofen as a cause of harm to either mother or fetus during pregnancy [Arthritis Advisory Committee, 1983; Barry et. al., 1984]. Non-steroidal anti-inflammatory drugs in general, however, are known to affect the action of prostaglandin synthetase which could alter a variety of the physiological functions of prostaglandins or platelets during delivery such as facilitating uterine contraction in the mother, closure of the ductus arteriosus in the fetus, and platelet-related haemostasis. Patients should therefore be advised not to use Children's MOTRIN® Cold during pregnancy without the advice of a physician, particularly during the last trimester. Clinical information is limited on the effects of ibuprofen in pregnancy.

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

Pediatrics (>6 months of age): Studies conducted to date have not demonstrated pediatric-specific problems that would limit the usefulness of ibuprofen in children 6 months and older. However, Children's MOTRIN® Cold is indicated in pediatric patients 4 years of age and older.

Geriatrics (> 65 years of age): Particular caution should be observed if elderly patients take Children's MOTRIN® Cold, as they are more likely to be taking other medications or have pre-existing disease states which can increase the likelihood of the complications that have been associated with ibuprofen. Elderly patients appear to be more susceptible to the effects of sympathomimetic amines and the central nervous system disease reactions; cognitive dysfunction (forgetfulness, inability to concentrate, a feeling of separation from the surroundings). These reactions have been reported in such patients.

Monitoring and Laboratory Tests

Not applicable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Pseudoephedrine may cause mild CNS stimulation, especially in patients who are hypersensitive to the effects of sympathomimetic drugs. Nervousness, excitability, restlessness, dizziness, weakness, and insomnia may occur. Headache and drowsiness have also been reported. Large doses may cause lightheadedness, nausea, and/or vomiting. In addition, the possibility of other adverse effects associated with sympathomimetic drugs, including fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse should be considered.

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.

Table 1 - Incidence of Adverse Events Attributed to Ibuprofen.

Adverse Effect	Incidence 3-9%	Incidence 1-3%
Gastrointestinal	▪ nausea ▪ epigastric pain ▪ heartburn	▪ diarrhea ▪ abdominal distress ▪ nausea and vomiting ▪ indigestion ▪ constipation ▪ abdominal cramps and pain ▪ gastrointestinal tract fullness (bloating or flatulence)
Central Nervous System	▪ dizziness	▪ headache ▪ nervousness

Dermatologic Special Senses Metabolic	▪ rash (including maculopapular type)	▪ pruritis ▪ tinnitus ▪ decreased appetite ▪ edema ▪ fluid retention (generally responds promptly to drug discontinuation)

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

Central Nervous System: Depression, insomnia.

Dermatologic: vesiculobullous eruptions, urticaria, erythema multiforme.

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

Cardiovascular: congestive heart failure in patients with marginal cardiac function, elevated blood pressure.

Allergic: Anaphylaxis.

Reports with an Unknown Causal Relationship

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

Special Senses: conjunctivitis, diplopia; optic neuritis.

Hematologic: hemolytic anemia; thrombocytopenia; granulocytopenia; bleeding episodes (e.g. purpura, epistaxis, hematuria, menorrhagia); auto-immune hematological anemia occurred in one patient taking 400 mg of ibuprofen three times a day for ten days; fatal aplastic anemia was reported in one patient who took 600 mg per day for 8 months.

Cardiovascular: arrhythmias (sinus tachychardia, sinus bradycardia, palpitations).

Allergic: fever, serum sickness, lupus erythematosus syndrome.

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

Renal: decreased creatinine clearance; polyuria; azotemia.

Abnormal Hematologic and Clinical Chemistry Findings

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

Hepatic: abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase)

Hematologic: leukopenia and decreases in hemoglobin and hematocrit
Renal: Renal blood flow glomerular filtration rate decreased in patients with mild impairment of renal functions who took 1200 mg/day of ibuprofen for one week.

Pseudoephedrine

Although oral administration of usual doses of pseudoephedrine to normotensive patients usually produced negligible pressor effects, the drug should be used with caution in hypertensive patients. Pseudoephedrine may increase the irritability of the heart muscle and may alter the rhythmic function of the ventricles, especially in large doses or when administered to patients who are hypersensitive to the myocardial effects of sympathomimetic drugs. Tachycardia or palpitation may occur. One patient who received 120 mg of pseudoephedrine hydrochloride every 4 hours developed multifocal premature ventricular contractions which disappeared a few days after the drug was discontinued. In addition, pseudoephedrine may have precipitated an attack of atrial fibrillation in an infant. It was postulated that the patient may have had previously unsuspected idiopathic atrial fibrillation, and therefore may have been especially sensitive to the myocardial effects of the drug.

Fixed dermatologic eruptions (erythematosus nummular patches) developed in 2 patients after a combination containing 60mg of pseudoephedrine hydrochloride and 2.5 mg of triprolidine hydrochloride was administered. Sensitivity testing indicated that pseudoephedrine was the cause of this reaction. In one patient with latent Horner's syndrome, administration of pseudoephedrine in combination with triprolidine caused ansocoria .

Post-Market Adverse Drug Reactions

Since the inception of marketing of combination ibuprofen/pseudoephedrine products, data from the United States shows that more than 3 billion doses have been administered in that country

alone. During the period between August 1, 2000 and July 31, 2004, 265 adverse drug reactions worldwide have been reported for Children's MOTRIN® Cold. A list of the reported adverse events is provided in the Table 2.

Table 2: U.S. Reported Adverse Events for Children's MOTRIN® Cold (August 1, 2000 to July 31, 2004)

Body System Adverse Event	**Number of Reported Events**
Body as a Whole	**8**
Aggravation Rxn - Autism (Worsening Symptoms)	1
Body Temperature Increased	1
Confusion	1
Fever	1
Headache	2
Malaise	1
Red Blood Cell Count Increased	1
Cardiovascular	**5**
Chest Pain	1
Heart Rate Increased / Tachycardia	4
Digestive	**40**
Abdominal Pain - General or Upper	8
Dyspepsia	3
Glossodynia	2
Nausea	2
Oral Discomfort	2
Retching	2
Vomiting	20
Vomiting Projectile	1
Endocrine	**3**
Aggravation Reaction - Diabetic (Increased Fasting Blood Sugars)	1
Goitre	1
Hyperglycemia	1
General Disorders / Administrative Site Conditions	**31**
Drug Ineffective / Lack of Effect / No Drug Effect	26
No Adverse Drug Effect	1
Reaction Unevaluable	3
Therapeutic Response Decreased	1
Hepatobiliary	**2**
Jaundice NOS	1
Liver Function Tests NOS Abnormal	1
Immune	**1**
Hypersensitivity NOS	1

Table 2: U.S. Reported Adverse Events for Children's MOTRIN® Cold (August 1, 2000 to July 31, 2004)

Body System Adverse Event	**Number of Reported Events**	
Injury, Poisoning and Procedural Complications		**15**
Accidental Exposure	6	
Accidental Overdose	7	
Medication Error	2	
Central Nervous System		**32**
Abnormal Gait	1	
Ataxia	1	
Convulsions	2	
Dizziness	1	
Dysgeusia	5	
Movement Disorder	1	
Nervousness	4	
Paresthesia	1	
Restlessness / Agitation	3	
Somnolence	9	
Speech Disorder	2	
Tremor	1	
Vasodilation	1	
Psychiatric		**16**
Abnormal Dreams	1	
Hallucinations	4	
Hostility / Irritability	2	
Insomnia	6	
Screaming / Screaming Syndrome	3	
Respiratory, Thoracic and Mediastinal		**19**
Apnea	1	
Asthma	3	
Dyspnea	2	
Epistaxis	3	
Hyperventilation	2	
Rhinitis	2	
Throat Irritation / Burning Throat	4	
Ulcer – Mouth	1	
Wheezing	1	
Skin and Appendages		**82**
Allergic Reaction (face - redness, itchiness; eyes and mouth - puffiness)	1	
Erythema	2	
Facial Edema / Swelling Face	17	
Pruritus (Generalized)	15	
Rash - Generalized or Pruritic	26	
Sweating	1	
Urticaria	19	
Vesiculobullous Rash	1	

Table 2: U.S. Reported Adverse Events for Children's MOTRIN® Cold (August 1, 2000 to July 31, 2004)

Body System Adverse Event	**Number of Reported Events**	
Special Senses – Eye		**10**
Eye Disorder NOS	1	
Eye(lid) Edema / Swelling	4	
Increased Blinking	1	
Irregular Eye Contact	1	
Ocular Icterus	1	
Vision Blurred	1	
Visual Disturbance NOS	1	
Urogenital		**1**
Abnormal Urine – Discolouration	1	

DRUG INTERACTIONS

Overview

Although ibuprofen binds to a significant extent to plasma proteins, interactions with other protein-bound drugs occur uncommonly. Nevertheless, caution should be observed when other drugs also having a high affinity for protein binding sites are used concurrently. Some observations have suggested a potential for ibuprofen to interact with furosemide, pindolol, digoxin, methotrexate, phenytoin and lithium salts. However, the mechanisms and clinical significance of these observations are presently not known. No interactions have been reported when ibuprofen has been used in conjunction with probenecid, thyroxine, steroids, antibiotics or benzodiazepines.

One manufacturer states that β-adrenergic blocking drugs such as propranolol may also increase the pressor effects of pseudoephedrine and that pseudoephedrine may reduce the anti-hypertensive effects of reserpine, methyldopa, mecamylamine hydrochloride, and veratrum alkaloids.

A general precaution is appropriate for patients to assure the compatibility of Children's MOTRIN® Cold with their other prescribed medications through consultation with a physician.

Drug-Drug Interactions

Serious Drug Interactions

- Use with acetylsalicylic acid (ASA) or other NSAIDs, including ibuprofen, may result in possible additive adverse side effects.
- Although interactions have not been reported, concurrent use with acetaminophen is not advisable; it may increase the risk of adverse renal effect.

- Use with anticoagulants may increase the risk of GI adverse events (e.g. bleeding).
- Use with hypoglycemic agents (oral agents and insulin) may increase the risk of hypoglycaemia.
- Use with antihypertensives may interfere with circulatory control.
- Use with diuretics may reduce the diuretic effect.
- Use with methotrexate may increase the risk of methotrexate toxicity.
- Use with lithium may increase the risk of lithium toxicity.

Coumarin Type Anticoagulants

Several short-term controlled studies failed to show that ibuprofen significantly affected prothrombin time or a variety of other clotting factors when administered to individuals on Coumarin-type anticoagulants. However, bleeding has been reported when ibuprofen and other NSAID agents have been administered to patients on Coumarin-type anticoagulants. The use of Children's MOTRIN® Cold in patients who are taking anticoagulants should therefore be avoided because of the possibility of enhanced GI bleeding or an additive effect due to ibuprofen's reversible anti-platelet actions.

Acetylsalicylic Acid

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

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

Other Anti-Inflammatory Agents (NSAIDs)

The addition of Children's MOTRIN® Cold to a pre-existent prescribed NSAID regimen in patients with a condition such as rheumatoid arthritis may result in increased risk of adverse effects.

Diuretics

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

Acetaminophen
Although interactions have not been reported, concurrent use with Children's MOTRIN® Cold is not advisable. Use with acetaminophen may increase the risk of adverse renal effect (see Warnings and Precautions – Renal).

Hypoglycemic Agents
Ibuprofen may increase hypoglycemic effects of oral anti-diabetic agents and insulin.

Sympathomimetic Agents
Pseudoephedrine should be administered with extreme caution, if at all, with other sympathomimetic agents because of the possibility of additive effects and increased toxicity.

Monoamine Oxidase Inhibitors
Monoamine oxidase (MAO) inhibitors, by increasing the quantity of norepinephrine in adrenergic nervous tissue, potentiate the pressor effects of indirectly acting sympathomimetic drugs such as pseudoephedrine. Infrequently, a hypertensive crisis may result. Pseudoephedrine should therefore be avoided in patients receiving drugs with MAO inhibiting activity.

Anti-hypertensives
NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, diuretics and NSAIDs might have an increased risk for acute renal failure and hyperkalemia.

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

Lithium
Monitoring of plasma lithium concentrations is advised when stopping or starting an NSAID, as increased lithium concentrations can occur.

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

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

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Weight		Age	Dose	
lbs	**kg**	**Years**	**mL**	**tsp**
Under 36	Under 16	Under 4*	Calculate based on weight and target ibuprofen dose of 7.5 mg/kg.	
36-47	16-21.9	4-5	5 mL	1 tsp
48-95	22-43.9	6-11	10 mL	2 tsp
Dose may be repeated every 6 hours, but not more than 4 times a day.				

*Consumer labelling does not offer dosing information for children under 4 years of age; this information is provided as a guide for professional recommendation to patients.

Children's MOTRIN® Cold should not be taken for more than 5 days. If symptoms do not improve, or are accompanied by fever that persists for more than 3 days, or if new symptoms occur, patient should consult a physician.

Do not give to children under 4 years of age, except as directed by a physician.

Missed Dose

If you miss a 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

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

OVERDOSAGE

Clinical Features

A clear pattern of clinical features associated with accidental or intentional overdose of ibuprofen has not been established. Reported cases of overdose have often been complicated by co-ingestions or additional suicidal gestures. The range of symptoms observed has included nausea, vomiting, abdominal pain, drowsiness, nystagmus, diplopia, headache, tinnitus, impaired renal function, coma and hypotension. A review of 4 fatalities associated with ibuprofen overdose indicates other contributing factors co-existed so it would be difficult to identify the toxicity of ibuprofen as a specific cause of death.

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

The following cases of overdose have been reported: A 19 month old child, 1-1/2 hours after the ingestion of 7 to 10 X 400 mg tablets of ibuprofen presented apnea, cyanosis and responded only to painful stimuli. After treatment with 0_2, $NaHCO_3$, infusion of dextrose and normal saline, the child was responsive and 12 hours after ingestion appeared completely recovered. Blood levels of ibuprofen reached 102.9 μg/mL, 8-1/2 hours after the accident. Two other children weighing approximately 10 kg, had taken an estimated 120 mg/kg. There were no signs of acute intoxication or late sequelae. In 1 child the ibuprofen blood level at 90 minutes after ingestion was approximately 700 μg/mL. A 19 year old male who ingested 8000 mg of ibuprofen reported dizziness and nystagmus was noted. He recovered with no reported sequelae after parenteral hydration and 3 days of bed rest.

For perspective, a single 200 mg oral dose study in 6 fasting healthy men produced a peak plasma concentration of 15.0 μg/mL at 0.75 hr. Another study using a single oral 400 mg dose in humans produced a peak serum level of 31.9 ± 8.8 μg/mL 0.5 hour after ingestion, and at 16 hours serum concentrations had dropped to 1 μg/mL. (See Pharmacology)

Management of Overdose

Appropriate interventions to decontaminate the gastrointestinal tract may be beneficial within the first 4 hours after ingestion. Routine symptomatic and supportive treatment is then recommended. Physicians should contact the Regional Poison Control Centre for additional guidance about ibuprofen overdose management.

Due to the rapid absorption of pseudoephedrine and ibuprofen from the gut, emetic and gastric lavage must be instituted within 4 hours of overdosage to be effective. Charcoal is useful only if given within 1 hour. Cardiac status should be monitored and the serum electrolytes measured. If there are signs of cardiac toxicity, propranolol may be administered intravenously. A slow infusion of a dilute solution of potassium chloride should be initiated in the event of a drop in the serum potassium level. Despite hypokalemia, the patient is unlikely to be potassium-depleted; therefore, overload must be avoided. Monitoring of the serum potassium is advisable for several hours after administration of the salt. For delirium or convulsions, intravenous administration of diazepan is indicated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ibuprofen is a member of the class of agents commonly known as non-steroidal anti-inflammatory drugs (NSAID). Like all NSAIDs, ibuprofen is an analgesic, antipyretic, and anti-inflammatory medication.

It is generally accepted that the basic mechanism of pharmacological action of ibuprofen, and other NSAIDs, is the inhibition of prostaglandin synthesis.

Nonselective NSAIDs (such as ibuprofen) and ASA act by inhibiting systemic (peripheral and central) prostaglandin G/H synthase isoenzymes, also known as cyclooxygenase-1 (COX-1) and

cyclooxygenase-2 (COX-2). These isoenzymes are responsible for the conversion of arachidonic acid to various tissue specific prostaglandins and thromboxanes. COX-1 is constitutively expressed in all tissues and is responsible for generating prostaglandins that maintain organ function, protect the integrity of the gastric mucosa and generate platelet-derived thromboxane responsible for platelet aggregation and vasoconstriction. During the inflammatory process COX-2 is induced, generating prostaglandins that mediate pain and inflammation. COX-2 is also present constitutively in the kidneys and vascular endothelium. Reported adverse experiences with ASA and other NSAIDs can be understood on the basis of this mechanism of action.

Pharmacodynamics

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

Pseudoephedrine: Pseudoephedrine acts directly on both α- and, to a lesser degree, β-adrenergic receptors. It is believed that α-adrenergic effects result from the inhibition of the production of cyclic adenosine-3', 5'-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas β-adrenergic effects result from stimulation of adenyl cyclase activity. Like ephedrine, pseudoephedrine also has an indirect effect by releasing norepinephrine from its storage sites.

Pseudoephedrine acts directly on α-adrenergic receptors in the mucosa of the respiratory tract producing vasoconstriction which results in shrinkage of swollen nasal mucous membranes, reduction of tissue hyperemia, edema, and nasal congestion, and an increase in nasal airway patency. Drainage of sinus secretions is increased and obstructed eustachian ostia may be opened.

Pseudoephedrine may relax bronchial smooth muscle by stimulation of β2-adrenergic receptors; however, substantial bronchodilation has not been demonstrated consistently following oral administration of the drug.

Oral administration of usual doses of pseudoephedrine to normotensive patients usually produces a negligible effect on blood pressure. Pseudoephedrine may increase the irritability of the heart muscle and may alter the rhythmic function of the ventricles, especially in large doses or after administration to patients such as those with cardiac disease who are hypersensitive to the myocardial effects of sympathomimetic drugs. Tachycardia, palpitation, and/or multifocal premature ventricular contractions may occur.

Pseudoephedrine may cause mild CNS stimulation, especially in patients who are sensitive to the effects of sympathomimetic drugs.

Pharmacokinetics

Absorption: Ibuprofen is rapidly absorbed after oral administration, with peak serum or plasma levels generally appearing within 1½ to 2 hours. Oral absorption is estimated to be 80% of the dose. Both the rate of absorption and peak plasma concentrations are reduced when the drug is taken with food but bioavailability as measured by total area under the concentration-time curve is minimally altered.

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

Pseudoephedrine is readily and almost completely absorbed from the GI tract and there is no evidence of first-pass metabolism. Following oral administration of a 60- or 120-mg dose of pseudoephedrine hydrochloride as an oral solution, peak plasma concentrations of about 180-300 or 397-422 ng/mL, respectively, were achieved in approximately 1.39-2 or 1.84-1.97 hours, respectively. Absorption from extended-release preparations is slower and peak plasma concentrations of the drug are achieved in about 3.8-6.1 hours. Following oral administration of single 30- or 60-mg doses of pseudoephedrine hydrochloride as a solution in pediatric patients (6-12 years of age), mean peak serum concentrations of 244 or 492 ng/mL, respectively, were achieved after 2.1 or 2.4 hours, respectively. Food delays absorption of the drug as a solution, but appears not to have an effect on absorption when the drug is administered as extended-release preparations.

Plasma pseudoephedrine concentrations of 274 ng/mL have been associated with a mean nasal decongestant response of 57.2%. Following oral administration of 60 mg of pseudoephedrine hydrochloride as tablets or oral solution, nasal decongestion occurs within 30 minutes and persists for 4-6 hours. Nasal decongestion may persist for 8 hours following oral administration of 60 mg and up to 12 hours following 120 mg of the drug in extended-release capsules.

Distribution: Clinical studies indicate a duration of clinical effect for ibuprofen of up to 8 hours for fever and 6 hours for pain.

Ibuprofen like most drugs of its class, is highly protein bound (>99% bound at 20 g/mL). Based on oral dosing data there is an age- or fever-related change in volume of distribution for

ibuprofen. Febrile children <11 years old have a volume of approximately 0.2 L/kg while adults have a volume of approximately 0.12 L/kg. The clinical significance of these findings is unknown. Tissue distribution of ibuprofen is also extensive in humans. Studies comparing synovial fluid levels with serum concentrations indicated that equilibration time post-ingestion occurred within approximately 3 to 5 hours.

Results of pre-clincal studies showed that pseudoephedrine is distributed to body tissues and fluids, including fetal tissue, breast milk and the central nervous system. Although specific clinical information is lacking, pseudoephedrine is presumed to cross the placenta and to enter CSF. Pseudoephedrine distributes into breast milk; about 0.5% of an oral dose is distributed into breast milk over 24 hours.

Metabolism: Ibuprofen is rapidly metabolized through oxidation and glucuronic acid conjugation with urinary excretion of the inactive metabolites usually complete within 24 hours. In humans, 84% is recoverable in the urine, primarily as conjugated hydroxy- and carboxy-metabolites, with only approximately l% excreted unchanged. Less than 10% is excreted in the urine. The 2 major metabolities of ibuprofen in humans have been found to have no activity in the ultraviolet erythema test in guinea pigs and in the acetylcholine-induced mouse writhing test at doses of l0 mg/kg and l5 mg/kg respectively.

Pseudoephedrine is incompletely metabolized in the liver (less than 1%) by N-demethylation to an inactive metabolite.

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

Pseudoephedrine and its metabolite are excreted in urine; 55-96% of a dose is excreted unchanged, with the remainder apparently metabolized in the liver to inactive compounds by N-demethylation, parahydroxylation and oxidative deamination. Urinary excretion of unchanged pseudoephedrine has been reported to be 70-90% of the administered dose within 24 hours. Urinary pH can affect the elimination half-life of pseudoephedrine, prolonging it when alkaline (pH 8) and reducing it when acidic (pH 5). The elimination half-life of pseudoephedrine ranges from 3-6 or 9-26 hours when urinary pH is 5 or 8, respectively. When urinary pH is 5.8, the elimination half-life of the drug ranges from 5-8 hours. In one study in children (6-12 years of age), the elimination half-life of pseudoephedrine averaged about 3 hours when urinary pH was 6.5. The rate of urinary excretion of pseudoephedrine is accelerated when urine is acidified to a pH of about 5 by prior administration of ammonium chloride. When the urine is alkalinized to a

pH of about 8 by prior administration of sodium bicarbonate, some of the drug is re-absorbed in the kidney tubule and the rate of urinary excretion is slowed.

Renal clearance of pseudoephedrine is about 7.3-7.6 mL/minute per kg in adults. Following oral administration of a single 30- or 60-mg dose of pseudoephedrine hydrochloride given as an oral solution in children (6-12 years of age), total body clearance was faster than that reported in adults, averaging about 10.3 or 9.2 mL/min/kg, respectively.

Special Populations and Conditions

Pediatrics: Although there is little evidence of clinically significant age dependent kinetics in febrile children ages 3 months to 12 years, some differences in the pharmacokinetic parameters of volume of distribution and clearance have been observed between adults and children.

Controlled clinical trials comparing doses between 5 and 10mg/kg of ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies, there were few differences between treatments in fever reduction in the first hour and maximum fever reduction occurred between 2 and 4 hours. There was some evidence that the higher dosage range of ibuprofen (10mg/kg) resulted in a prolonged duration of effect (from 6 to 8 hours) and that it was more effective for children with higher baseline temperatures (above 102.5^{o}F/39.1°C) but the numbers of patients were not adequate to draw definitive conclusions. In children with baseline temperatures at or below 102.5^{o}F (39.1°C) both ibuprofen doses and acetaminophen were equally effective in their maximum effect.

Following oral administration of a single 30 or 60 mg dose of pseudoephedrine hydrochloride as a solution in children (6-12 years of age), the mean apparent volume of distribution at steady-state was 2.6 or 2.4 L/kg, respectively. The steady–state volume of distribution from the multiple dose study was 2.5 L/kg.

A multiple dose pharmacokinetic study was conducted to describe the steady-state pharmacokinetics of pseudoephedrine HCl and ibuprofen in assessing the potential for a drug interaction between pseudoephedrine and ibuprofen. Table 3 summarizes study results. A total of five doses were administered. Single doses were administered every 6 hours and each dose provided 7.5mg/kg ibuprofen and 1.125mg/kg psuedophedrine HCl. Neither drug accumulated considerably and no interaction between ibuprofen and pseudoephedrine observed.

TABLE 3 *IN VIVO* PHARMACOKINETIC DATA[A] FOR IBUPROFEN AND PSEUDOEPHEDRINE HCL WHEN ADMINISTERED IN COMBINATION AS A SUSPENSION

Ingredient	AUCτ (µg·h/mL)	$C_{MAX,ss}$ (µg/mL)	$C_{MAX,1}$ (µg/mL)	$T_{MAX,SS}$ (h)	$T_{MAX,1}$ (h)	Cl/F (mL/h/kg)	Vd/F (L/kg)	k_A (1/h)	k_{EL} (1/h)	t½ (h)
Ibuprofen	99.3	32.0	29.6	0.97	1.02	77.5	0.15	1.887	0.546	1.3
Pseudoephedrine	1276	295	218	1.39	1.68	12.3	2.5	1.417	0.303	2.5

AUCτ : area under the curve of the dosing interval at steady state

$C_{MAX,1}$: maximum plasma concentration after the first dose
$T_{MAX, SS}$: time to reach maximum plasma concentration at steady state
$T_{MAX,1}$: time to reach peack concentration after the first dose
Cl/F: oral clearance
Vd/F : apparent Volume of distribution
k_A : absorption rate constant
k_{EL} : elimination rate constant
t½ : elimination half-life

Geriatrics: Studies demonstrate no apparent clinically significant alterations in ibuprofen pharmacokinetics in the elderly.

Hepatic Insufficiency: Ibuprofen pharmacokinetics has been studied in patients with alcoholic liver disease who have been assessed to have fair to poor hepatic function. Results suggest despite the liver being the primary organ of metabolism of ibuprofen, its kinetic parameters are not substantially altered by this condition.

STORAGE AND STABILITY

Stability studies were conducted on the product in HDPE bottles with Polypropylene caps. The recommended storage condition is: Store at room temperature, 15°C to 30°C (59°F to 86°F).

SPECIAL HANDLING INSTRUCTIONS

None.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Children's MOTRIN® Cold is available in Berry, Grape and Dye-Free Berry in a 120 mL bottle:

Medicinal Ingredients: 100 mg/5 mL ibuprofen
15 mg/5 mL pseudoephedrine HCl

Non-Medicinal Ingredients:

Berry Flavour

- Acesulfame K
- Citric Acid
- D&C Yellow No. 10
- FD&C Red No. 40
- Glycerin
- N&A Cherry Berry Flavour
- Polysorbate 80
- Pre-Gelatinized Starch
- Purified Water
- Sodium Benzoate
- Sucrose
- Xanthan Gum

Grape Flavour

- Artificial Grape Flavour
- Acesulfame K
- Citric Acid
- D&C Red No. 33
- FD&C Blue No.1
- FD&C Red No. 40
- Glycerin
- Polysorbate 80
- Pre-Gelatinized Starch
- Purified Water
- Sucrose
- Sodium Benzoate
- Xanthan Gum

Dye-Free Berry

- Acesulfame K
- Citric Acid
- Glycerin
- N&A Cherry Berry Flavour
- Polysorbate 80
- Pre-Gelatinized Starch
- Purified Water
- Sodium Benzoate
- Sucrose
- Xanthan Gum

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

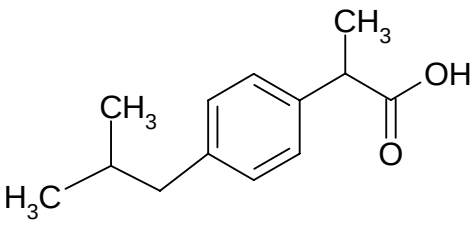
Drug Substance

Proper name: Ibuprofen

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

Molecular formula and molecular mass: $C_{13}H_{18}O_2$, 206.3

Structural formula:



Physicochemical properties:

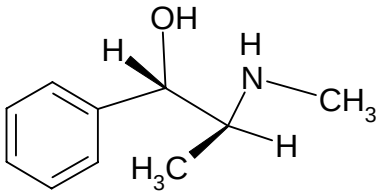
- White crystalline powder with a characteristic odour and slight taste
- Soluble:
  - 1 in 1.5 of alcohol
  - 1 in 1 of chloroform
  - 1 in 2 of ether
  - 1 in 1.5 of acetone
  - in aqueous solution of alkali hydroxides and carbonates.
- Very slightly soluble in water and very soluble in alcohol and other common organic solvents
- Apparent pKa 5.2.

Proper name: pseudoephedrine hydrochloride

Chemical name: [S-(R*,R*)]-α-[1(methylamino)ethyl]-Benzenemethanol hydrochloride

Molecular formula and molecular mass: $C_{10}H_{15}NO,HCl$, 201.7

Structural formula:



▪ H Cl

Physicochemical properties:

- Soluble in:
  - water
  - alcohol
  - chloroform.
- pH (1 in 20 solution): 4.6 - 6.0
- Melting Point: 180-186 °C

CLINICAL TRIALS

Safety

Study demographics and trial design

An open-label, multiple-dose pediatric outpatient clinical safety study using the ibuprofen-pseudoephedrine suspension product (Children's MOTRIN® Cold) was conducted.

Table 4 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
99-086	Open-label study of the safety of an ibuprofen-pseudoephedrine HCl suspension [a] in children	**Dosage**: Ibuprofen 6.3 - 9.2 mg/kg and Pseudoephedrine 0.9 - 1.4 mg/kg. **Route:** Oral suspension **Duration:** up to 3 days.	114 patients	5.8 years (2-11)	Male and Female

a) Administered as Children's MOTRIN® Cold Suspension

Of the 114 subjects in the study, 53.5% were male, 65.8% were Caucasian, 33.3% were between 2-3 years of age, 68.4% were below 7 years of age, and 30.7% weighted between 10.9 –15.9 kg.

Study results

Table 5 - Results of study 99-086 in specific indication

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
To describe the safety profile of a pediatric ibuprofen/pseudoephedrine HCl combination suspension product in children with symptoms of the common cold, flu or sinusitis.	Overall 13.2% of subjects reported drug related adverse events, and most were of mild to moderate intensity.	Not applicable.

The number and percent of subjects with drug-related adverse events are shown in Table 6. One or more drug-related adverse events were reported by 13.2% of subjects. The most common adverse event was somnolence, reported by 7.0% of subjects.

Table 6: Number (Percent) of Subjects With Drug-Related Adverse Events, McNeil Study 99-086

Body System Adverse Event[a]	All Subjects (N = 114) n (%)
Any adverse event	**15 (13.2)**
Body as a whole	**2 (1.8)**
Abdominal pain	2 (1.8)
Digestive	**1 (0.9)**
Nausea	1 (0.9)
Nervous	**11 (9.6)**
Hyperkinesia	1 (0.9)
Insomnia	1 (0.9)
Nervousness	1 (0.9)
Somnolence	8 (7.0)
Respiratory	**1 (0.9)**
Cough increased	1 (0.9)
Skin and appendages	**1 (0.9)**
Urticaria	1 (0.9)

[a] Includes all adverse events noted as definitely, probably, or possibly drug-related and adverse events of unknown relationship to study drug.

Comparative Bioavailability Studies

A three-way single dose comparative bioavailability study was conducted in adults comparing the rate and extent of absorption of Children's MOTRIN® Cold with single ingredient reference

products. The ibuprofen reference product used in the study was Children's MOTRIN® Ibuprofen Suspension. The pseudoephedrine reference product used in the study was Children's Sudafed® Nasal Decongestant Liquid (US). There were no statistically significant differences for any pharmacokinetic variables concluding bioequivalence of the treatments. Summary tables of comparative bioavailability data for ibuprofen and pseudoephedrine are presented in Tables 7 and 8, respectively.

Table 7: Summary table of comparative bioavailability data for ibuprofen**

Ibuprofen (1 x 7.5 mg/kg) **Geometric Mean** **Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90 % Confidence Intervals**
AUC_T (µg·h/mL)	199 202 (19)	179 181 (17)	111	105 - 118
AUC_I (µg·h/mL)	201 205 (19)	181 183 (18)	111	105 - 118
C_{MAX} (µg/mL)	60.7 61.9 (20)	59.0 60.3 (21)	103	94.6 - 112
T_{MAX} (h)	0.70 (36)	0.74 (46)		
$T_{½}$ (h)	2.2 (12)	2.2 (13)		

* Children's MOTRIN® Cold Suspension
† Children's MOTRIN® Ibuprofen Suspension, McNeil Consumer Healthcare, (USA).
** In 24 healthy subjects

Table 8: Summary table of comparative bioavailability data for pseudoephedrine**

Pseudoephedrine (1x 15 mg/5 mL) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Intervals
AUC_T (µg·h/mL)	2199 2223 (15)	2098 2125 (16)	105	101 - 109
AUC_I (µg·h/mL)	2568 2614 (19)	2566 2633 (23)	100	95.3 - 105
C_{MAX} (µg/mL)	320 322 (11)	272 273 (10)	118	113 - 123
T_{MAX} (h)	1.48 (50)	2.60 (27)		
$T_{½}$ (h)	4.7 (20)	5.1 (25)		

* Children's MOTRIN® Cold Suspension
† Children's Sudafed® Nasal Decongestant Liquid (Pseudoephedrine HCl)
** In 24 healthy subjects

Clinical Trials:

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

Dental Pain

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

Sore Throat or Ear Pain (Pediatric Models)

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

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

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

Dysmenorrhea

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

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

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

Pain of Osteoarthritis

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

Headache

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

Soft Tissue Injury

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

Fever

Studies of its efficacy in the management of fever in adults and children demonstrate ibuprofen to be an effective antipyretic, with a duration of action of up to 8 hours when administered at a dose of 7.5 mg/kg.

One controlled clinical trial comparing a single dose of ibuprofen 7.5 mg/kg with acetaminophen 12.5 mg/kg demonstrated the superiority of ibuprofen over an 8 hour period.

DETAILED PHARMACOLOGY

Ibuprofen

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

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

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

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

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

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

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

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

Pseudoephedrine

Pseudoephedrine is a vasopressor with a potency in dogs of approximately one fifth that of ephedrine, with more pronounced tachyphylaxis. The positive inotropic and chronotropic effects of pseudoephedrine in dogs are less than those of ephedrine.

Pressor responses, as well as increased heart rate, induced by pseudoephedrine in anesthetized dogs are reduced by reserpinization.

Pseudoephedrine constricts all systemic blood vessels in dogs with the exception of the vertebral and renal vessels; the latter blood vessels are dilated by pseudoephedrine.

The bronchodilating potencies of pseudoephedrine and ephedrine in anesthetized dogs are approximately equal, but pseudoephedrine produces a greater degree of nasal decongestion with less cardiovascular involvement than ephedrine.

Doses as high as 200 mg/kg (i.p.) do not increase locomotor activity in mice, but do reduce wheel-revolving activity. Rectal temperature is decreased by 50 mg/kg doses of pseudoephedrine, whereas 200 mg/kg, temperature is first decreased and subsequently increased. Pseudoephedrine does not alter pentobarbital sleep-time. The effects of pseudoephedrine on the central nervous system are clearly weaker than those of ephedrine, and may involve different mechanisms.

MICROBIOLOGY
Not applicable.

TOXICOLOGY

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

Single graded doses of ibuprofen were administered by oral intubation or by intraperitoneal or subcutaneous injection to groups of l0 male albino mice and male albino rats. Gross reactions were observed and mortalities recorded over a period of l4 days. The LD_{50} values determined by this method were 800 mg/kg orally and 320 mg/kg intraperitoneally in the mouse and l600 mg/kg orally and l300 mg/kg subcutaneously in the rat. Acute signs of poisoning were prostration in mice, and sedation, prostration, loss of righting reflex and laboured respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration.

Similar LD_{50} determinations in other strains of rats and mice are summarized in Table 9.

Table 9 - Acute Toxicity in Rodents (LD_{50})

Species	Route	LD_{50} Range (mg/kg)
Albino Mice[ab]	Oral Intraperitoneal	800-1000 320
Albino Rats[a]	Oral Subcutaneous	1600 1300
Sprague Dawley Rat[c]		1050
Long Evans Rat[d]		1000

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

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

Another group studied the production of gastrointestinal lesions in the rat comparing ulcerogenic doses of ibuprofen and other NSAIDs after oral or intravenous administration. Both male and female Long Evans rats were used in all experiments. Prior to drug administration the animals were fasted for 8 hours. After treatment they were fed a normal diet and sacrificed after l7 hours. Gastric and intestinal mucosa was examined for presence of ulcers. The ulcerogenic dose in 50% of treated animals (UD_{50}) was calculated. The UD_{50} following oral administration of ibuprofen was determined to be 70 mg/kg while for intravenous ibuprofen it was 210 mg/kg. The intestinal UD_{50} was 88 mg/kg following oral and 172 mg/kg with intravenous administrations. A calculated "severity index" of gastric lesions was higher by the oral than the IV route at all doses tested.

Studies of the ulcerogenic potential of ibuprofen are summarized in Table 10.

Table 10 - Single Dose Ulcerogenicity Studies in Rodents

Species	Route	UD50*(mg/kg)	MUD**(mg/kg)
Long Evans Rat[a]	Oral IV	70 210	50 -
Sprague Dawley Rat[b]	Oral	-	6-13

*ulcerogenic dose in 50% treated animals
**minimum ulcerogenic dose
[a]Cioli et al., 1980
[b]Atkinson and Leach, 1976

Various single oral doses of ibuprofen were administered to dogs with subsequent hematologic examination and biochemical analyses of blood and urine, and examination of feces for occult

blood. Gross examination of the major organs occurred after the animals were sacrificed. No ill effects were seen following doses of 20 or 50 mg/kg. Oral doses of 125 mg/kg or greater produced emesis, scouring, albuminuria, fecal blood loss and erosions in the gastric antrum and pylorus.

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

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

Similar studies of multiple dose ulcerogenic potential of ibuprofen are summarized in Table 11.

Table 11 - Multiple Oral Dose Toxicity Studies

Species	Daily Dose	Duration	Ulcerogenic Factor
Albino Rat[a]	400mg/kg	30 hours	Ulcers in 100%
Albino Rat[b]		4 days	UD50 = 455 mg/kg/day UD28 = 240 mg/kg/day
Long Evans Rat[c]		5 days	MUD = 25 - 50 mg/kg/day
Sprague Dawley Rat[d]	5.8-225 mg/kg	10 days	None
Albino Rat[e]	7.5mg/kg 180mg/kg	26 weeks 26 weeks	None Ulcers in 20%
Dog[e]	4mg/kg 8mg/kg 16mg/kg	30 days 30 days 30 days	None 100% 100%

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

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

Chronic toxicity studies in dogs demonstrated no gross or clinical signs of toxicity at 4, 8 or 16 mg/kg/day for 30 days. However, in all dogs given 8 or 16 mg/kg/day, postmortem examination revealed gastric ulcers or erosions. No lesions were observed in dogs given 4 mg/kg/day.
A more complete assessment of chronic toxicity of ibuprofen in dogs studied the effects of administration of oral doses of 0, 2, 4 or 26 mg/kg/day over 26 weeks. Periodic blood, urine and

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

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

Teratogenicity studies of ibuprofen have been conducted in rabbits and rats [Adams, Bough et al., 1969]. Results of the experiments indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits nor is there embryotoxic or teratogenic activity in pregnant rats even when administered in ulcerogenic doses.

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

Pseudoephedrine Hydrochloride

Mice injected with toxic doses of pseudoephedrine manifest increased motor activity, penile erection, mydriasis, and eventually die in respiratory exhaustion. The intravenous LD_{50} in mice is approximately 90 mg/kg.

The approximate oral LD_{50} values for several species are 726 mg/kg (mouse), 2,206 mg/kg (rat), 1,117 mg/kg (rabbit), 105 mg/kg (beagle dog) and 307 mg/kg (mongrel dog). Toxic effects in these species include decreased respiratory activity, salivation and lacrimation, loss of pupillary reflex reaction to light, tremor, convulsions and cardiac arrhythmias.

Ibuprofen and Pseudoephedrine Hydrochloride

The oral toxicity of combinations of ibuprofen and pseudoephedrine were evaluated in mice and rats. The LD_{50} values derived from these studies are listed in Table 12. From these values, it was concluded that the combinations tested have a relatively low order of toxicity.

Table 12 - LD_{50} values for Ibuprofen and Pseudoephedrine Hydrochloride Combinations

Combination	Rats LD_{50} (Range)	Mice LD_{50} (Range)
Ibuprofen 200 mg Pseudoephedrine 30 mg	1.4 (1.4-1.5)	2.4 (1.7-3.4)
Ibuprofen 400 mg Pseudoephedrine 60 mg	1.4 (1.3-1.6)	1.2 (0.42-2.9)
Ibuprofen 200 mg	0.85 (0.68-1.06)	1.8 (1.3-2.5)

A study was conducted to evaluate the potential toxic and teratogenic effects of the combination product and its individual components, ibuprofen and pseudoephedrine hydrochloride when administered orally to pregnant rats during the period of major organogenesis. Three groups of 25 mated female rats were each administered the fixed combination of dosage levels of 11.5, 34.5 and 115 mg/kg/day. Two additional groups, composed of identical numbers of animals were dosed with the individual components, (ibuprofen and pseudoephedrine) at levels of 100 and 15 mg/kg/day, respectively. The control group received the vehicle, 1% aqueous methylcellulose. The animals were treated for 10 consecutive days from gestation day 6 through 15. During the study, the animals were observed daily for occurrence of changes in external appearance and behaviour. Body weight and food intake were measured on gestation days, 0, 6, 9, 12, 16, and 20. Cesarean section was performed on gestation day 20. The fetuses were weighed and examined for external visceral, skeletal developmental malformations and variations.

Neither the combination drug product, nor its components, ibuprofen and pseudoephedrine hydrochloride, affected maternal survival at dosage levels employed in this study. Mean maternal body weight gains and food consumption were reduced during the treatment period in the high dose combination of (115 mg/kg/day) and ibuprofen (100 mg/kg/day) groups when compared with the control group. Increased incidence of enlarged mesenteric lymph nodes was observed in the high-dose combination (115 mg/kg/day), ibuprofen (100 mg/kg/day) and pseudoephedrine (15 mg/kg/day) groups when compared to the control group. The biological significance of this finding is unknown.

Mean numbers of viable and dead fetuses, early and late resorption, as well as mean fetal weights were comparable between the control and all treated groups. The occurrence of developmental malformations and variations were similar among the control and the treated animals

No clinical sign of maternal or fetal toxicity having teratogenic effects were observed at the dosage levels selected for this study.

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PART III: CONSUMER INFORMATION
Children's MOTRIN® Cold
ibuprofen and pseudoephedrine hydrochloride
oral suspension

100 mg/5 mL ibuprofen and
15 mg/5 mL pseudoephedrine hydrochloride

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

ABOUT THIS MEDICATION

What the medication is used for:
Relief of symptoms associated with sinusitis, the common cold or flu including:
- **Stuffy Nose**
- **Sinus Pressure**
- **Sinus Pain**
- **Fever**
- **Body Aches & Pains**
- **Sore Throat Pain**
- **Headache**

What it does:
Ibuprofen is a pain reliever and fever reducer and pseudoephedrine hydrochloride is a nasal decongestant.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs block the production of prostaglandins that are involved in pain and fever development.

Pseudoephedrine hydrochloride acts on receptors in the respiratory mucosa. This helps to shrink swollen nasal membranes and to relieve congestion.

When it should not be used:
Do not use Children's MOTRIN® Cold in patients who:
- **are taking acetylsalicylic acid (ASA), other NSAIDs, other ibuprofen- or pseudoephedrine-containing products or any other pain or fever medicine.**
- **are allergic to ibuprofen, pseudoephedrine hydrochloride, products containing ASA, other NSAIDs or salicylates or any ingredient in the formulation (see What the nonmedicinal ingredients are).**
- **have ASA-sensitive asthma, active or recurrent stomach or intestinal ulcer, gastrointestinal (GI) bleeding or active inflammatory bowel disease (e.g. Crohn's, colitis), liver or kidney disease and/or suffered significant fluid loss (i.e. diarrhea, dehydration), high blood pressure or heart disease, hyperkalemia (high potassium levels) or Systemic Lupus Erythematosus.**
- **are pregnant, nursing or taking a prescription monoamine oxidase inhibitor (MAOI - drugs for depression, psychiatric or emotional conditions or Parkinson's disease) or for two weeks after stopping an MAOI drug.**

What the medicinal ingredients are:
Ibuprofen and Pseudoephedrine Hydrochloride

What the nonmedicinal ingredients are:
(To be supplied as appropriate for the formulation)

Berry: acesulfame potassium, citric acid, corn starch, D&C yellow #10, FD&C red #40, flavours, glycerin, polysorbate 80, purified water, sodium benzoate, sucrose, xanthan gum.

Dye Free Berry: acesulfame potassium, citric acid, corn starch, flavours, glycerin, polysorbate 80, purified water, sodium benzoate, sucrose, xanthan gum.

Grape: acesulfame potassium, citric acid, corn starch, D&C red #33, FD&C blue #1, FD&C red #40, flavours, glycerin, polysorbate 80, purified water, sodium benzoate, sucrose, xanthan gum

What dosage forms it comes in:
Children's MOTRIN® Cold is available in Berry, Grape and Dye-Free Berry in a 120 mL bottle.

WARNINGS AND PRECAUTIONS

BEFORE giving Children's MOTRIN® Cold to your child, talk to your doctor or pharmacist if:
- **your child is dehydrated (significant fluid loss) due to continued vomiting, diarrhea or lack of fluid intake.**
- **your child has peptic ulcers or a history of peptic ulcers, stomach bleeding or other**

bleeding problems, GI tract irritation or is prone to GI tract irritation, diabetes, glaucoma, high blood pressure, thyroid or heart disease, serious kidney or liver disease, asthma, blood problems (low white or red blood cell count), bladder problems (pain, frequent urination, infection) or is pregnant, nursing, under a doctor's care for any other serious condition or taking any other drug.

Also, see to your doctor if:
- **your child does not get any relief within 24 hours.**
- **a sore throat is severe, lasts for more than 2 days or occurs with fever, headache, rash, nausea or vomiting.**
- **if any new symptoms appear**

Always tell any other doctor or pharmacist you consult, that your child is taking this medicine.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if your child is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric/emotional conditions, Parkinson's disease), or for 2 weeks after stopping a MAOI drug. If you are uncertain that your prescription drug contains a MAOI, talk to your doctor before taking this product.

Talk to a doctor before using Children's MOTRIN® Cold if your child is taking ASA or other NSAIDs, blood thinning medications (anticoagulants), blood pressure medication (anti-hypertensives), diuretics (water pills), lithium, diabetes medications (hypoglycemics), decongestant or stimulant products (sympathomimetic agents), methotrexate, phenytoin, digoxin, oral glucocorticoids or any other pain or fever medicine (such as acetaminophen).

PROPER USE OF THIS MEDICATION

Shake well before using. Use only enclosed measuring cup. Replace original bottle cap to maintain child resistance.

Use the chart below to find the correct dose. If possible, use weight to dose, otherwise use age.

Weight		Age	Single Oral Dose	
lbs.	**kg**	**Years**	**mL**	**tsp**
Under 36	Under 16	Under 4	As directed by your doctor.	
36-47	16-21.9	4-5	5 mL	1 tsp
48-95	22-43.9	6-11	10 mL	2 tsp

Doses may be repeated every 6 hours, up to 4 times a day.

Do not use Children's MOTRIN® Cold for children under 4 years of age, unless instructed by your doctor.

If stomach upset occurs, take with food or milk. If the stomach upset does not go away, talk to your doctor.

Children's MOTRIN® Cold should not be taken for more than 5 days. If symptoms do not improve, or are accompanied by fever that persists for more than 3 days, if new symptoms occur, or if your child feels nervous, dizzy or cannot sleep, stop use and consult your doctor.

<u>Overdose</u>:
Call a Poison Control Centre or doctor at once, even if there are no symptoms.

<u>Missed Dose:</u>
If you miss a dose, take the missed dose as soon as you remember. Do not take two doses at the same time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

- **nausea, vomiting, abdominal pain or diarrhea; heartburn; bloating; constipation; fluid retention; skin rash, itching or high fever; dizziness; any change in vision; ringing or buzzing in the ears.**

Ibuprofen may cause a severe allergic reaction that could include: facial swelling, hives, wheezing, shortness of breath, shock or a fast, irregular heartbeat. Any of these reactions could be serious. If they occur, stop using this product and get emergency medical help immediately.

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

HOW TO STORE IT

Store at room temperature, 15°C - 30°C (59°F to 86°F). . Do not keep medicine that is outdated (after the expiry date).

Keep this medication out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.website.document
or by contacting the sponsor, McNeil Consumer Healthcare, Division of Johnson & Johnson Inc. at:
1-888-6MOTRIN (1-888-666-8746)

This leaflet was prepared by McNeil Consumer Healthcare, Division of Johnson & Johnson Inc.

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