PRODUCT MONOGRAPH

COLD & SINUS RELIEF CAPSULES

Ibuprofen (free acid and potassium salt) and Pseudoephedrine Hydrochloride Capsules

200 mg / 30 mg

Professed Standard

Analgesic/Antipyretic/Nasal Decongestant

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Table of Contents

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Ibuprofen and Pseudoephedrine Hydrochloride Capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	Liquid Filled Soft Gel Capsule: ibuprofen 200 mg (present as free acid and potassium salt), pseudoephedrine hydrochloride 30 mg	Each capsule contains D&C Yellow no.10, FD&C Red no.40, gelatin, polyethylene glycol, potassium hydroxide, propylene glycol, and sorbitol sorbitan solution. The sorbitol sorbitan solution contains sorbitan, sorbitol, mannitol and high polychains. The capsule shells are imprinted with black edible ink and contain the non-medicinal ingredients: hypromellose, iron oxide black and propylene glycol.

INDICATIONS AND CLINICAL USE

COLD & SINUS RELIEF CAPSULES are indicated for:

- the temporary relief of symptoms associated with the common cold, including nasal congestion, sore throat pain, headache, fever, and minor body aches and pains.

COLD & SINUS RELIEF CAPSULES are non-prescription analgesic and nasal decongestant preparations.

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. Therefore the use of COLD & SINUS RELIEF CAPSULES in this population is not recommended. (*See Warnings and Precautions and Dosage and Administration*).

Children (<12 years of age):
COLD & SINUS RELIEF CAPSULES is not indicated for children <12 years of age.

CONTRAINDICATIONS

- Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system, such as ulcerative colitis and Crohn's disease.

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

- COLD & SINUS RELIEF CAPSULES should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom angioedema syndrome, asthma, anaphylaxis, bronchospastic reaction, urticaria, rhinitis or other allergic manifestations are precipitated by acetylsalicylic acid (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.

- 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 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 *(See Drug Interactions)*.

- Children (i.e. 18 years of age and younger) with kidney disease and children who have suffered significant fluid loss due to vomiting, diarrhea or lack of fluid intake, should not be given ibuprofen.

- COLD & SINUS RELIEF CAPSULES should not be used by patients who have known or suspected hypersensitivity to pseudoephedrine or other sympathomimetic amines, are taking or have taken monoamine oxidase inhibitor (MAOI) drugs within the last 14 days, have been diagnosed with severe hypertension, or have severe coronary artery disease [59] *(See Drug Interactions).*

- Ibuprofen should not be used during pregnancy or by nursing mothers.

- 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.

- Known hyperkalemia (see Warnings and Precautions – Renal – Fluid and Electrolyte Balance)

- Immediately before or following heart surgery.

- In patients with thyroid disease.

- In patients with Raynaud's Syndrome.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Patients with glaucoma or difficulty in urination due to enlargement of the prostate gland should not take this drug unless directed by a physician [154] (See *WARNINGS AND PRECAUTIONS, General*).
- 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 who might be prone to gastrointestinal tract irritation, particularly those with a history of 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, Coumarin-type anticoagulants*).
- Caution in patients at greatest risk of renal toxicity, such as 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*).>

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

If nervousness, dizziness, or sleeplessness occurs, use of COLD & SINUS RELIEF CAPSULES should be discontinued and a physician should be consulted. COLD & SINUS RELIEF CAPSULES should not be used for more than 3 days for fever or 5 days for cold symptoms/pain.

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.

COLD & SINUS RELIEF CAPSULES should be used with caution in hypertensive patients because of the possible pressor effect of pseudoephedrine. Pseudoephedrine has been shown to increase blood pressure in normotensive adults and in patients with hypertension.

Pseudoephedrine treatment may increase heart rate and can cause arrhythmia. Asymptomatic, multifocal premature ventricular contractions (PVCs) were reported with the use of Actifed® (a combination of pseudoephedrine with an antihistamine, triprolidine), two tablets every 4 hours around the clock, for several days to treat nasal congestion [62]. The PVCs disappeared within a few days after discontinuation of the medication.

Dependence/Tolerance
Pseudoephedrine has the potential to cause drug dependency and withdrawal effects. Reportedly, a woman with a history of depression experienced a stimulatory effect from the use of 50 to 300 mL of Actifed® (pseudoephedrine and triprolidine) daily (the recommended dose is 30 mL per day) [70]. A 37-year-old woman admitted to taking 100 to 150 30-mg pseudoephedrine tablets daily [71]. She had gradually increased the daily dose over the previous 5 years to counteract chronic fatigue, apathy, and depression. A previous attempt to discontinue use of the drug had produced visual hallucinations, severe fatigue, and depression. Slow withdrawal by 200 to 300 mg/day resulted in a return of depressive symptoms; thereafter, the dose was decreased more slowly, by 90 mg/day. The patient was later diagnosed as having a mixed character disorder and reactive depression.

Ear/Nose/Throat
See *Contraindications*.

Endocrine and Metabolism
Patients with thyroid disease should not take this drug. See *Contraindications*.

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

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

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

COLD & SINUS RELIEF CAPSULES 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, COLD & SINUS RELIEF CAPSULES 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. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anticoagulant use have been associated with increased risk. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

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

Ischemic colitis has been reported in association with the use of pseudoephedrine. In four separate cases, perimenopausal women had ingested varying quantities of pseudoephedrine (60 mg or more daily) for treatment of upper respiratory disorders [60]. All patients had taken pseudoephedrine within the week preceding symptom onset, and all patients presented with complaints of acute onset abdominal pain associated with fresh blood in the stool. Colonoscopy revealed in each case a segmental colitis characterized by oedematous, hyperaemic colonic mucosa, most often in the region of the splenic flexure, yet also extending upward to involve the transverse colon. Several occurrences of frank mucosal haemorrhage were observed. Biopsy samples of mucosa revealed acute inflammatory changes consistent with ischemic colitis. In each case, the patient recovered without further incident or recurrence after pseudoephedrine was discontinued.

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 COLD & SINUS RELIEF CAPSULES must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anticoagulants or suffering from haemophilia or platelet disorders, should be carefully observed when ibuprofen is administered.

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 (AST, ALT, alkaline phosphatase) 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 and liver necrosis 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
Patients with complete or partial syndrome of nasal polyps, rhinitis or other allergic manifestations should not use ASA or other anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals even if they have taken NSAIDs in the past without any adverse effects (See *Contraindications*).

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

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.

High plasma concentrations of phenylalanine in individuals with phenylketonuria may exacerbate the CNS effects of pseudoephedrine.

Ophthalmologic
Blurred and/or diminished vision has been reported with the use of ibuprofen and other nonsteroidal 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 be closely monitored.

Peri-Operative Considerations
See *Contraindications*. In general NSAIDs are discontinued prior to surgeries to decrease the risk of post-operative bleeding [153].

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 interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

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

Ibuprofen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with impaired renal function. In these cases, utilisation of lower doses of COLD & SINUS RELIEF CAPSULES should be considered and patients carefully monitored.

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

Pseudoephedrine and its active metabolite are excreted chiefly via the kidneys [31]. 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 60 mg of pseudoephedrine four times daily for 12 days to treat nasal congestion [65].

Respiratory
Patients with asthma should not use ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals even if they have taken NSAIDs in the past without any adverse effects (See *Contraindications*).

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
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.

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 skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Special Populations

Pregnant Women:

COLD & SINUS RELIEF CAPSULES 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 COLD & SINUS RELIEF CAPSULES to women who are trying to conceive, during the first and second trimesters of pregnancy, or if breastfeeding (see Toxicology).

Nursing Women: COLD & SINUS RELIEF CAPSULES is contraindicated for use during nursing.

Pediatrics: COLD & SINUS RELIEF CAPSULES is not indicated for children less than 12 years of age.

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 acetylsalicylic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product. Most reports of fatal GI events are in this population. Older patients are also at risk of lower oesophageal ulceration and bleeding. There is also increased susceptibility to effects of sympathomimetic amines observed in elderly patients.

COLD & SINUS RELIEF CAPSULES is not indicated for use in patients over 65 years of age.

Monitoring and Laboratory Tests
For *Warnings and Precautions* related to the use of Ibuprofen and pseudoephedrine hydrochloride capsules and *Monitoring and Laboratory Tests* see *Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal a*nd *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.

Adverse Events in Clinical Studies of Ibuprofen and pseudoephedrine hydrochloride.

Three studies of Ibuprofen (100 mg) and pseudoephedrine hydrochloride (15 mg) were conducted in a total of 156 children 2 to 11 years of age (mean age, 5.9 years). In one of the studies, 104 children took the medication for up to 7 days to treat symptoms of upper respiratory infection. The mean number of days of treatment was 4.8. The other two studies were single-dose pharmacokinetic studies. One child withdrew from the multiple-dose study because of episodes of feeling "shaky." The symptom resolved after study medication was discontinued.

In combined data from the three studies, the most frequently reported adverse events were somnolence (in seven children), vomiting (in three children), and otitis media (in three children) (Table 1). Only two adverse events were considered severe: somnolence in one child, which lasted for about 1 hour and was considered remotely related to study medication, and ear pain, which resolved within 2 days without treatment and was considered unrelated to study medication. All other adverse events were considered mild or moderate in intensity.

Table 1 Adverse Events in Clinical Studies of ibuprofen (100 mg) and pseudoephedrine hydrochloride (15 mg)

Body System	COSTART Term	Number (%) of Subjects Reporting Event (N = 156)
Body as a whole	Asthenia	2 (1%)
	Fever	2 (1%)
	Back pain	1 (<1%)
	Common cold	1 (<1%)
	Headache	1 (<1%)
	Pain	1 (<1%)
	Chills	1 (<1%)
Digestive	Vomiting	3 (2%)
	Abdominal pain	2 (1%)
	Nausea	2 (1%)
	Diarrhoea	1 (<1%)
	Dyspepsia	1 (<1%)
Haemic and lymphatic	Lymphadenopathy	1 (<1%)
	Lymphocytosis	1 (<1%)
Nervous	Somnolence	7 (4%)
	Tremor	2 (1%)
	Hyperkinesia	1 (<1%)
	Nervousness	1 (<1%)
Respiratory	Rhinitis	2 (1%)
Skin and appendages	Pruritus	1 (<1%)
	Rash	2 (1%)

Special senses	Otitis media	3	(2%)
	Conjunctivitis	1	(<1%)
	Ear disorder	1	(<1%)
	Ear pain	1	(<1%)

Safety Studies of Ibuprofen and Pseudoephedrine Combination
In patients with upper respiratory infections treated with either ibuprofen 200 mg plus pseudoephedrine 30 mg (n = 294), acetaminophen 500 mg (n = 296), or placebo (n = 146), the frequency of adverse events (mostly gastrointestinal and CNS symptoms) was similar among the three treatment groups [78].

In a placebo-controlled, double-blind clinical study of 58 subjects with rhinovirus infection, pseudoephedrine given alone or with ibuprofen was well tolerated [79]. Symptoms associated with sympathetic stimulation tended to be more frequent in subjects who were treated with pseudoephedrine (60 mg, either alone or with 200 mg ibuprofen) than in those who received placebo. The three treatment groups were similar in mean pulse rate and mean blood pressure.

Safety Studies of Ibuprofen
The results of a double-blind, placebo-controlled study in healthy subjects (N = 1246) representative of a non-prescription analgesic user population indicate that ibuprofen at a dosage of 1200 mg/day for 10 consecutive days is well tolerated [80]. The frequency of gastrointestinal adverse experiences was similar in the placebo and ibuprofen groups (16% with placebo vs. 19% with ibuprofen). The most frequent gastrointestinal adverse experiences (those reported by 1% of the subjects) were dyspepsia, abdominal pain, nausea, diarrhoea, flatulence, and constipation. There was no difference between the two groups in the proportion discontinuing treatment because of gastrointestinal adverse events. Seventeen subjects (1.4%) had positive occult blood tests: the frequency was comparable for the two treatments.

In two multitrial analyses [81, 82], a meta analysis [83], and a literature review [84], ibuprofen had a low incidence of gastrointestinal drug reactions, comparable with that of acetaminophen and placebo. In epidemiological studies, ibuprofen has consistently exhibited the lowest relative risk of severe gastrointestinal complications compared with other NSAIDs and acetylsalicylic acid [85, 86, 87]. No symptom or syndrome emerged in the trials that was not predicted from the drug's pharmacology or could not have been anticipated based on ibuprofen's extensive use as an analgesic/antipyretic in adults.

Garcia-Rodriguez reported on the frequency of acute liver injury among 625,307 people who received NSAIDs in England and Wales between 1987 and 1991, of whom 311,716 were prescribed ibuprofen [88]. The incidence of acute liver injury among ibuprofen users was 1.6/100,000. This was the lowest incidence among the eight NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were simultaneous use of hepatotoxic medication and the presence of rheumatoid arthritis.

Two large-scale safety studies of ibuprofen examined the potential risk in children of several rare events that are related to the pharmacological action of NSAIDs: GI bleeding, acute renal failure, and anaphylaxis.

The Children's Analgesic Medicine Project (CAMP) was a multicenter, all-comers, open-label, nonrandomized, prospective study comparing the safety of ibuprofen suspension with acetaminophen suspension in children with fever and/or pain [155]. A total of 424 paediatricians enrolled children at

69 US clinics; 14,281 were <2 years of age and 15,863 were 2 to <12 years of age. Among children <2 years of age, fever, vomiting, diarrhoea, rhinitis, rash, and otitis media were the only adverse events with frequency >1% in either treatment group (ibuprofen or acetaminophen). Among children 2 years of age, the only adverse events with frequency >1% in either treatment group were rhinitis, pharyngitis, and otitis media. Adverse events were generally mild to moderate for both treatments within the two age groups. There were no serious adverse events, (no anaphylaxis, Reye syndrome, renal failure, or GI bleeding/perforation). The percentage of younger children with adverse events was slightly higher in the ibuprofen group (17.6% vs. 15.0%); similar results were seen in the older children (11.9% vs. 10.7%). The difference may have been due to the preference of physicians to treat the sicker children with ibuprofen. Overall, ibuprofen exhibited an adverse event profile similar to that of acetaminophen.

The Boston Fever Study was a randomized, double-blind study that assessed the risk of rare but serious adverse events after the use of ibuprofen suspension in febrile children between 6 months and 12 years of age [89, 90, 91]. The study evaluated a total of 83,915 children enrolled by 1735 paediatricians, family physicians, and general practitioners in the United States. Children were randomly assigned to receive ibuprofen suspension 5 mg/kg (N = 27,948), ibuprofen suspension 10 mg/kg (N = 27,837), or acetaminophen suspension 12 mg/kg (N = 28,130). Medications were given every 4 to 6 hours, as needed, for a total of up to five doses per day. The study recorded hospitalisations for acute GI bleeding, acute renal failure, and anaphylaxis and monitored for the occurrence of Reye syndrome. In the entire 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.

Adverse Events with Doses of Ibuprofen ≥1200 mg/day

Gastrointestinal
In clinical trials of NSAIDs, symptomatic upper GI ulcers, gross bleeding, or perforation occurred in approximately 1% of patients treated for 3 to 6 months and in about 2 to 4% of patients treated for 1 year. The risk continues beyond 1 year. The incidence of GI complications increases with increasing dose.

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 <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 <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 <1%: depression, insomnia. Causal relationship unknown: paraesthesias, hallucinations, abnormal dreams.

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 <1%: vesiculobullous eruptions, urticaria, erythema multiforma. Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

Cardiovascular
Incidence <1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations. Causal relationship unknown: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations).

Special Senses
Incidence 1 to 3%: tinnitus. Incidence <1%: amblyopia (blurred and/or diminished vision, scotomata, and/or changes in colour vision). Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

Haematologic
Incidence <1%: leukopenia, decreases in haemoglobin and haematocrit. Causal relationship unknown: haemolytic anaemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g., purpura, epistaxis, haematuria, menorrhagia).

Hepatic
Liver enzyme elevations may occur in up to 15% of patients treated with ibuprofen.

Renal
Acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome have been reported. Renal papillary necrosis has been reported. Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia.

Endocrine
Causal relationship unknown: gynecomastia, hypoglycaemic reaction. Menstrual delays of up to 2 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.

Post-Market Adverse Drug Reactions

Spontaneously Reported Adverse Events for Ibuprofen/Pseudoephedrine Products
Since the inception of marketing of combination ibuprofen/pseudoephedrine products, more than 3 billion doses have been distributed in the United States alone. During the period from 1989 to 2000, Whitehall-Robins received 411 reports describing 699 adverse drug reactions world wide for all marketed products containing ibuprofen and pseudoephedrine in combination. Fifty-three of the reports were associated with a serious outcome, usually hospitalisation. One death was reported; in the reporter's opinion, the death was related to staphylococcal septicaemia and not to ibuprofen/ pseudoephedrine. Table 2 lists the events that were spontaneously reported three or more times, by body system and preferred term from a coding dictionary (COSTART in most cases; also MedDRA).

Table 2 Adverse Events Reported Spontaneously Three or More Times with use of Ibuprofen/Pseudoephedrine-Containing Products Marketed by Whitehall-Robins (August 1989-December 31, 2000)

Body System	Preferred Term	Number of Events
Body as a whole		
	Allergic reaction	13
	Anaphylaxis	3
	Asthenia	11
	Fever	6
	Headache	9
	Malaise	4
	No drug effect	132
	Oedema, face	14
	Overdose	3
	Pain	7
	Pain, abdomen	10
	Reaction, aggravated	6
	Reaction, unevaluated	9
Cardiovascular system		
	Fibrillation, atrial	3
	Haemorrhage, cerebral	3
	Hypertension	12
	Hypotension	3
	Ischemia, cerebral	3
	Palpitations	6
	Tachycardia	5
	Vasodilation	12
Digestive system		
	Diarrhoea	4
	Dyspepsia	11
	Melena	4
	Nausea	17
	Vomiting	9
Haemic and lymphatic	Purpura, thrombopenic	3
	Thrombocytopenia	4
Metabolic and nutritional	Oedema, peripheral	3
Musculoskeletal	Twitch	6
Nervous system		
	Dizziness	29
	Euphoria	4
	Insomnia	26
	Nervousness	16
	Paraesthesia	4
	Somnolence	13
	Tremor	3
Respiratory system	Asthma	3
	Dyspnoea	10
	Epistaxis	5
	Rhinitis	10
Skin and appendages	Angioedema	9

Table 2 Adverse Events Reported Spontaneously Three or More Times with use of Ibuprofen/Pseudoephedrine-Containing Products Marketed by Whitehall-Robins (August 1989-December 31, 2000)

Body System	Preferred Term	Number of Events
	Pruritus	22
	Rash	30
	Rash, maculopapular	12
	Sweating	5
	Urticaria	15
Special senses	Diplopia	4
	Parosmia	3
	Tinnitus	3
	Vision abnormal	3
Urogenital system	Urinary retention	6

Safety Data on Pseudoephedrine From Case Reports

Hyperthermia
A 21-year-old man who was taking pseudoephedrine for weight loss died suddenly after receiving heat-phenol-inactivated typhoid vaccine and Japanese encephalitis vaccine [92]. While on a 3-mile run 75 minutes after the inoculation, he collapsed and was found pulseless and apnoeic. He was in asystole, with a rectal temperature of 42.2ºC. External pacing, cooling, and resuscitation efforts were unsuccessful. There was no evidence of urticaria, angioedema, heart failure, thrombosis, cerebral oedema, or petechial haemorrhage. The sympathomimetic effects of pseudoephedrine may have decreased the cooling ability of the body and increased susceptibility to heat-related adverse effects. The combined pyrogenic effects of the vaccines, exercise, mild obesity, and an impaired thermoregulatory system may have contributed to the patient's death.

Cardiovascular Adverse Reactions
Hypertension and loss of consciousness were reported in a 17-year-old man within 30 minutes after ingestion of one tablet of pseudoephedrine 60 mg [93]. Blood pressure on admission was 170/110 mmHg, pulse was 124 beats per minute, and the patient was unresponsive to painful stimuli. Approximately 1 hour after ingestion of pseudoephedrine, the patient awoke spontaneously. Blood pressure was 124/80 mmHg; pulse was 96 beats per minute. Pseudoephedrine may have induced a state of relative cerebral ischemia secondary to carotid vasoconstriction.

Postural hypotension was reported in a 28-year-old male airplane pilot after administration of pseudoephedrine 60 mg three times daily for 2 days. Physical examination revealed a supine blood pressure of 115/74 mmHg, which fell to 96/60 upon standing and was associated with dizziness lasting 10 to 15 seconds. Symptoms disappeared after discontinuation of pseudoephedrine and recurred upon rechallenge [94].

Pseudoephedrine was reported to cause coronary artery spasm and myocardial infarction in a 28-year-old man [95]. The patient took 30 mg pseudoephedrine for rhinitis and experienced chest pressure. The next night he took an additional 60 mg and had crushing chest pressure. An electrocardiogram showed ST-segment elevation consistent with a myocardial infarction, and cardiac enzymes were elevated. The pain and electrocardiographic changes resolved after administration of sublingual nitroglycerin.

Dermatologic Adverse Reactions
Brownstein reported two cases of fixed-type skin eruptions after use of Actifed®, a combination of pseudoephedrine with an antihistamine, triprolidine [96]. The rashes subsided within a few days after the medication was discontinued but reappeared after the patients again ingested Actifed. One of the two patients was challenged three times with 50-mg doses of pseudoephedrine. Each time, the rash recurred at the same sites. A fixed drug eruption was described in a 48-year-old woman on two occasions after administration of pseudoephedrine [97]. Indurated erythematous plaques developed on the right upper eyelid, elbows, antecubital fossae, axillae, and lower legs. The lesions were mildly pruritic. Discontinuance of pseudoephedrine and corticosteroid therapy resulted in clearing of the eruption on both occasions. Two similar cases of pseudoephedrine-induced fixed drug eruptions have been reported [98].

In multiple separate episodes over the course of 19 years, a man developed intense pruritus of the fingers about 12 hours after ingesting pseudoephedrine-containing products [99]. This was followed by severe redness, swelling, heat, and white papules on the fingers. The swelling subsided after 7 days and was followed by desquamation lasting about 2 weeks.

After ingesting medication containing triprolidine plus 60 mg pseudoephedrine, a 10-year-old boy developed an oedematous, erythematous plaque [100]. The lesion cleared within 2 weeks and reappeared at the same site after rechallenge with 30 mg pseudoephedrine.

Pseudoephedrine was associated with pseudo-scarlatina in a 32-year-old woman [101]. The reaction recurred after rechallenge with pseudoephedrine.

Other Types of Adverse Reactions
Severe agitation, screaming, and confusion occurred in a 10-month-old infant with phenylketonuria after administration of pseudoephedrine 15 mg every 6 hours for treatment of acute otitis media. Symptoms were noted within 1 hour after the first dose and recurred after each dose for two subsequent doses. After discontinuation of pseudoephedrine, no further episodes occurred. The patient's plasma concentration of phenylalanine, which had previously ranged from 2 to 7 mg/dL, increased to 12 mg/dL during the illness [162].

An 18-year-old woman developed symptoms presenting as recurrent toxic shock syndrome after ingesting pseudoephedrine-containing cold preparations and after a challenge with 60 mg pseudoephedrine [102]. She remained symptom-free for 1 year, during which she avoided pseudoephedrine-containing medications. When she inadvertently used a cough syrup containing pseudoephedrine, she again developed toxic shock symptoms.

DRUG INTERACTIONS

Serious Drug Interactions

- With acetaminophen may increase the risk of adverse renal effect.
- With acetylsalicylic acid (ASA), other NSAIDs including ibuprofen 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 (insulin and oral agents) 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.
- With monoamine oxidase inhibitors may result in hypertensive crisis and other serious adverse reactions (See *Contraindications*).

Overview

COLD & SINUS RELIEF CAPSULES is not recommended for concomitant use with any other NSAIDs, including ASA and other ibuprofen. Documented or possible drug interactions with Ibuprofen and pseudoephedrine hydrochloride include acetaminophen, digoxin, anticoagulants, oral antidiabetic agents and insulin, antihypertensives, diuretics, methotrexate, lithium, and other protein-bound drugs.

Drug-Drug Interactions

The drugs listed in this section are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (*i.e.,* those identified as contraindicated).

Acetaminophen

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

Acetylsalicylic acid (ASA) or other NSAIDs

The use of COLD & SINUS RELIEF CAPSULES in addition to any other NSAID, including ASA, is not recommended due to the possibility of additive side effects. Animal studies show that acetylsalicylic acid given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-acetylsalicylic acid drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of acetylsalicylic acid on ibuprofen blood levels. Correlative clinical studies have not been conducted (See *Contraindications*).

Antacids [82]

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.

Anticoagulants [77,78]

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 COLD & SINUS RELIEF CAPSULES to patients on anticoagulants.

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 [149, 150] 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 [151] showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β-adrenergic blockers. Houston et al. [152] 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.[145] 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.[146] In contrast, Minuz [147] 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.

Cough-cold/allergy Medications:
The use of other decongestants, cough and cold medications, allergy medications or medications containing pseudoephedrine or ibuprofen should be avoided as it can increase the risk of serious side effects and overdose.

Digoxin [148]
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 [75]
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 [74]
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.

Monoamine Oxidase Inhibitors
COLD & SINUS RELIEF CAPSULES should not be used concomitantly with MAO inhibitors or for 14 days after stopping the MAOI drug. MAO inhibitors are prescribed for treatment of depression, psychiatric or emotional conditions, or Parkinson's disease. Hypertensive crisis and other serious adverse reactions have been reported in patients using pseudoephedrine or other sympathomimetic drugs such as ephedrine in combination with or shortly after discontinuing MAO inhibitors [134, 135] (See *Contraindications*).

Other Drugs
COLD & SINUS RELIEF CAPSULES should be used with caution when other drugs, also having a high affinity for protein binding sites, are used concurrently. However, while ibuprofen binds extensively to plasma proteins, interactions with other protein-bound drugs occur rarely. Caution should be used when taking COLD & SINUS RELIEF CAPSULES in conjunction with probenecid, thyroxine, cyclosporine, antibiotics (e.g. levofloxacin), 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.

Drug-Lifestyle Interactions
Avoid drinking alcohol while taking COLD & SINUS RELIEF CAPSULES, as this may increase the risk of serious stomach bleeding. Avoid smoking while taking Ibuprofen and pseudoephedrine hydrochloride capsules or other NSAIDs.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Do not take for fever for more than 3 days or for more than 5 days for cold symptoms/pain.
Patients older than 65 years should not use COLD & SINUS RELIEF CAPSULES.

Recommended Dose and Dosage Adjustment

Adults under 65 years of age and children over 12 years of age: Take 1 or 2 capsules every 4 to 6 hours as needed. Maximum 6 capsules in 24 hours, unless directed by a physician.

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 Overdosage
COLD & SINUS RELIEF CAPSULES contain ibuprofen and pseudoephedrine hydrochloride. The toxicity of overdose is dependent upon the amount of the product ingested and the time elapsed since ingestion; individual responses may vary, thus making it necessary to evaluate each case separately. The most frequently reported symptoms of the two combination drugs in situations of overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness, headache, tinnitus, CNS depression, seizures, anxiety, hyper-excitability, irritability, delirium, convulsions, dilated pupils, tachycardia, bradychardia, hypertension or hypotension, atrial fibrilation, abnormal speech, visual and tactile hallucinations, ataxia, and hyper-reflexia. Metabolic acidosis, electrolyte disturbances, coma, acute renal failure, and apnoea (primarily in very young children) may rarely occur.

Treatment of Overdosage
In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Due to the rapid absorption of pseudoephedrine and ibuprofen from the gut, emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption of drugs 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 [144]. Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. 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 diazepam is indicated.

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 [103]. 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 [104]. 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 [105]. A 6-yearold child became comatose after ingesting 6 g of ibuprofen [106]. He was treated with gastric lavage, charcoal, and various supportive measures and recovered within 24 hours.

Examples of Pseudoephedrine Overdose
Hypertensive crisis (blood pressure 200/160 mmHg) was reported in a 23-year-old man after ingestion of 840 mg pseudoephedrine (in Trinalin® tablets; also containing azatadine). The patient presented with severe headache, dizziness, diaphoresis, and epigastric pain. His hypertension was treated effectively with intravenous labetalol [107].

In a study to determine the toxicity of pseudoephedrine in children 2 to 6 years of age, 22% of 101 exposures to doses ranging from 30 to 180 mg were associated with drowsiness, and 7% were associated with mild hyperactivity [108]. The symptoms were mild, and the children were treated with fluids and observation. Of 39 exposures to doses above 180 mg, 15% were associated with drowsiness and 13% were associated with mild hyperactivity.

Hypertension was reported in an 8-week-old infant after administration of pseudoephedrine 7.5 mg four times daily orally and phenylephrine 1/4% intranasally four times daily for 7 days. The infant's blood pressure normalized after discontinuation of the decongestants and remained normal at follow-up [109].

A 2-year-old boy was overdosed with a non-prescription cough and cold preparation containing 7.5 mg dextromethorphan and 15 mg pseudoephedrine per 5 mL [110]. After receiving three doses of 1.5 teaspoonfuls spaced 6 hours apart, he developed hyperexcitability, hyperirritability, agitation, incoherent babbling, and difficulty maintaining his balance. On examination, the patient exhibited hyperactivity, ataxia, dilated pupils, and tachycardia (180 beats per minute). His status normalized over a period of 4 hours.

A 3-year-old girl experienced visual hallucinations after administration of a non-prescription decongestant containing pseudoephedrine [111]. The child had inadvertently been given 20 mg/kg of pseudoephedrine administered in two doses over the previous 12 hours. A 5 year old boy suffered from severe hallucinations beginning 5 hours after drinking 60 mL of syrup containing pseudoephedrine and triprolidine (Actifed®) [112].

Pseudoephedrine overdose may precipitate psychosis in individuals with underlying psychiatric disorders.

A 27-year-old man with a history of bipolar affective disorders experienced an episode of acute paranoid psychosis after chronic abuse of Actifed® syrup (pseudoephedrine and triprolidine) [113]. The patient had abused Actifed® for several years, taking one to two bottles on weekends. Approximately 4 days prior to onset of visual and auditory hallucinations and paranoia, he had increased the amount to two bottles per day. His hallucinations disappeared within 1 day after discontinuation of Actifed®.

A mixed bipolar psychotic disorder was precipitated by a large dose of pseudoephedrine in a 13-year-old girl with a familial predisposition to psychotic disorders [114]. The patient took 8 tablets of 60 mg pseudoephedrine in one afternoon. She was hospitalized for psychiatric treatment and was

discharged after 2 weeks. She had another psychotic episode 7 months later, without exposure to pseudoephedrine.

A 19-month-old girl who ingested approximately 600 mg of pseudoephedrine experienced a generalized tonic clonic seizure [115].

Examples of Ibuprofen/Pseudoephedrine Hydrochloride Combination Products Overdose

In seven of eight reports of overdose with an ibuprofen/pseudoephedrine hydrochloride combination, the patients recovered without hospitalisation. A 17-year-old woman ingested eight tablets of ibuprofen/pseudoephedrine hydrochloride combination plus 24 to 30 tablets of extra strength Tylenol®. She was treated with Mucomyst and charcoal and was discharged from the hospital after a 2-day stay [117].

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ibuprofen
Like other nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen is an analgesic, antipyretic, and anti-inflammatory medication [1]. The principal mechanism of action of ibuprofen and other NSAIDs is inhibition of prostaglandin biosynthesis [2, 3]. Prostaglandins contribute to fever, pain, and inflammation by sensitizing tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The committed step in prostaglandin biosynthesis is catalyzed by prostaglandin endoperoxide synthase, also known as cyclooxygenase [4]. NSAIDs decrease prostaglandin biosynthesis by inhibiting cyclooxygenase.

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 [143].

Pseudoephedrine Hydrochloride
Pseudoephedrine acts directly on both alpha- and, to a lesser degree, beta-adrenergic receptors [16]. It is believed that alpha-adrenergic effects result from inhibition of the production of cyclic adenosine-3', 5'-monophosphate (AMP) by inhibition of the enzyme adenyl cyclase, whereas beta-adrenergic

effects result from stimulation of adenyl cyclase activity. Like ephedrine, pseudoephedrine also acts indirectly by releasing norepinephrine from its storage sites [16].

Pseudoephedrine acts directly on alpha-adrenergic receptors in the mucosa of the respiratory tract, producing vasoconstriction that results in shrinkage of swollen nasal mucous membranes, reduction of tissue hyperaemia, oedema, and nasal congestion, and, thereby, an increase in nasal airway patency [16]. Drainage of sinus secretions is increased, and obstructed eustachian ostia may be opened [16].

Pharmacokinetics

Absorption:

Ibuprofen
Ibuprofen is a racemic mixture of R-(-) ibuprofen and S-(+) ibuprofen. R-(-) ibuprofen undergoes extensive (53% to 65%) enantiomeric conversion to S-(+) ibuprofen in humans [5]. S-(+) ibuprofen is the pharmacologically active enantiomer.

Ibuprofen is rapidly absorbed after oral administration. Serum concentrations reach a peak within 1 to 2 hours in adults [4] and in children [6, 7, 8]. Food decreases the rate but not the extent of ibuprofen absorption [4].

Pseudoephedrine Hydrochloride
After oral administration, pseudoephedrine is readily and completely absorbed from the gastrointestinal tract, with no evidence of first-pass metabolism [16, 17]. After oral administration of syrups containing 60 mg or 120 mg of pseudoephedrine, peak plasma pseudoephedrine concentrations of 180 ng/mL to 422 ng/mL, respectively, were obtained at 1 to 2 hours [18, 156, 19, 20].

In a study of five children aged 6 to 12 years receiving 2 mg/kg of pseudoephedrine up to a maximum dose of 60 mg, the peak concentration (C_{max}) was 338 ng/mL, T_{max} was 1.86 hours, and $t_{1/2}$ was 4.61 hours [21]. More recently, Simons et al characterized the pharmacokinetics of pseudoephedrine in children with seasonal allergic rhinitis [157]. The results are presented in Table 3.

Table 3 Pharmacokinetics of Pseudoephedrine in Children with Seasonal Allergic Rhinitis (Mean Age, 8.8 Years)

Pharmacokinetic Parameter	Pseudoephedrine 30 mg (N = 7)	Pseudoephedrine 60 mg (N =7)
C_{max} (ng/mL)	244± 21	492±72
TMAX (H)	2.1±0.3	2.4±0.2
$t_{1/2}$ (h)	3.1±0.5	3.1±0.4
AUC (ng/mL/h)	1260±126	2414±336
Cl (mL/min/kg)	10.3±1.2	9.2±0.7
Vdss (L/kg)	2.6±0.3	2.4±0.4

Note: Values are means standard error of the mean (SEM). AUC = area under the plasma concentration versus time curve, Cl = clearance, Vdss = steady-state volume of distribution.

The absorption rate of pseudoephedrine, as measured by its urinary excretion rate, is significantly increased by the concurrent administration of aluminium hydroxide gel, is decreased by kaolin, and is unaffected by sodium bicarbonate [23]. Food appeared to delay absorption of pseudoephedrine from

syrup formulations and controlled-release capsules but had no effect on absorption from a suspension [156, 20].

Distribution:

Ibuprofen
After oral administration, the volume of distribution of ibuprofen was 0.1 to 0.2 L/kg in adults [9] and 0.18 to 0.22 L/kg in febrile children [6]. At therapeutic concentrations, ibuprofen is extensively bound to whole human plasma and binds primarily to site II of purified albumin [9].

Pseudoephedrine Hydrochloride
The volume of distribution of pseudoephedrine ranged from 2.64 L/kg to 3.51 L/kg in single- and multiple-dose studies [24, 25]. Pseudoephedrine concentration-time data after oral administration are well described using a one body compartment model with first-order absorption and elimination [24, 25]. The approximate plasma clearance of pseudoephedrine is 0.44 L/h/kg [24].

Metabolism:

Ibuprofen
The plasma half-life (t½) of ibuprofen in adults and children is 1.5 2.0 hours [6, 10]. There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses [4]. 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 in urine [11,12]. Parent drug and metabolites are excreted primarily in the urine. Bile and faeces are relatively minor elimination routes. Approximately 80% of an ibuprofen dose is recovered in urine within 24 hours, primarily as carboxymetabolites and hydroxymetabolites, both conjugated and unconjugated [9].

Cytochrome P450 (CYP) 2C9 has been identified as the most important enzyme in the oxidative metabolism of R-(-) and S-(+) ibuprofen [13]. Ibuprofen does not appear to induce the formation of drug-metabolizing enzymes in rats [12].

There is no evidence of changes in metabolism or elimination of ibuprofen with advanced age. A pharmacokinetic evaluation of ibuprofen in subjects 65 to 78 years of age compared with young adult subjects (22 to 35 years of age) found no clinically significant difference in the pharmacokinetic profiles of ibuprofen for the two age groups [14]. Furthermore, there was no statistically significant difference between the two age groups in the urinary excretion pattern of the drug and its major metabolites. The pharmacokinetic results for ibuprofen in children are similar to findings in adults.

Pseudoephedrine Hydrochloride
Less than 1% of pseudoephedrine is eliminated by hepatic metabolism. The major biotransformation of pseudoephedrine is N-demethylation to the active metabolite norpseudoephedrine [17].

Because pseudoephedrine is a weak base, with a pKa of 9.2, its half-life is dependent on urinary pH. The serum half-life increases as urine pH increases, varying from 1.9 hours at pH 5.6 to 21 hours at pH 7.8 [31, 32]. At urine pH greater than 7.0, pseudoephedrine is extensively reabsorbed in the renal tubules, and therefore its excretion rate is dependent on urine flow rate. Higher flow rates decrease the intratubular drug concentration and the time for reabsorption, leading to greater renal clearance. When urine pH is acidic, renal reabsorption is negligible and urine flow does not influence clearance of the drug.

In a study in children in which the urine pH was 6.5, pseudoephedrine had a shorter half-life (3.1 hours) and faster clearance (9.2 to 10.3 mL/min/kg) than in studies of similar design in adults in which the urine pH was not controlled or reported [157]. Fifty-six percent of the pseudoephedrine dose was recovered in the urine within 12 hours, and an additional 10% was recovered over the period from 12 to 24 hours.

The shorter terminal elimination half-life of pseudoephedrine in children may reflect greater renal tubular secretion or reabsorption in children than in adults. The faster clearance rate and smaller volume of distribution in children than in adults is probably due to the relatively lower lean body mass in children [157]. Over the 30-mg to 60-mg dose range, the kinetics of pseudoephedrine in children were not dose dependent [33].

Excretion:

Ibuprofen
Ibuprofen is rapidly excreted in breast milk. Thirty minutes after oral ingestion of 400 mg of ibuprofen, the concentration in breast milk was found to be 13 ng/mL [15]. The milk:plasma ratio was 1:126, and the exposure of a suckling infant to ibuprofen was calculated to be approximately 0.0008% of the maternal dose [15]. Studies in animals indicate that ibuprofen is transported across the placenta.

Pseudoephedrine Hydrochloride
Pseudoephedrine is excreted largely unchanged in urine, with 43% to 96% recovered in 24 hours [23, 26, 27, 28, 29, 30]. Norpseudoephedrine recovery from urine ranged from less than 1% to 6.2% [26, 20, 31].

Pseudoephedrine is presumed to cross the placenta and to enter the cerebrospinal fluid [34]. Approximately 0.4% to 0.7% of an oral dose is excreted in breast milk over 24 hours [35]. Pseudoephedrine levels two to three times higher in milk than in plasma have been reported [35]. Adverse effects (irritability, excessive crying, disturbed sleeping patterns) were reported in a breast-fed infant whose mother had received pseudoephedrine [36]. The symptoms resolved within 12 hours after discontinuation of pseudoephedrine.

STORAGE AND STABILITY

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

Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each peach coloured liquid-filled gelatin capsule contains 200 mg ibuprofen (present as free acid and potassium salt) and 30 mg pseudoephedrine hydrochloride. The liquid-filled gelatin capsules are available in blister packages of 10, 20 and 30 capsules and bottles of 40 and 50 capsules.

In addition to the active ingredients, ibuprofen and pseudoephedrine hydrochloride, each capsule contains the non-medicinal ingredients: D&C Yellow no.10, FD&C Red no.40, gelatin, polyethylene glycol, potassium hydroxide, propylene glycol, and sorbitol sorbitan solution.

The sorbitol sorbitan solution contains sorbitan, sorbitol, mannitol and high polychains.

The capsule shells are imprinted with black edible ink and contain the non-medicinal ingredients: hypromellose, iron oxide black and propylene glycol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Ibuprofen

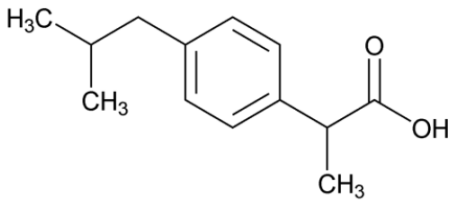
Proper Name: Ibuprofen

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

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

Molecular Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.28 g/mol

Structural Formula:



Physicochemical Properties:

Physical Characteristics: White or almost white powder or crystals with a characteristic odour.

Solubility: Low solubility in water (<0.1 mg/mL), 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 value: pKa = 4.43

Melting Point: 75°C to 77°C

Pseudoephedrine Hydrochloride

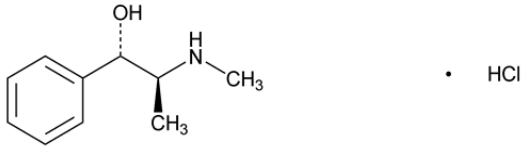
Proper Name: Pseudoephedrine hydrochloride

Chemical Name: {S-(R*, R*)-α -{1-(methylamino)ethyl} benzenemethanol hydrochloride

Other names: (+)-Pseudoephedrine hydrochloride

Molecular Formula: $C_{10}H_{15}NO.HCl$
Molecular Weight: 201.69 g/mol

Structural Formula:



Physicochemical Properties:

Physical characteristics: White powder or crystals

Solubility: Soluble in water, alcohol, and chloroform

pKa and pH values: pKa = 9.2, pH = 5.9 in an aqueous solution of 1 in 200

Melting Point: 180°C to 186°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male and female volunteers. The results obtained from 16 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of Ibuprofen and Pseudoephedrine were measured and compared following a single oral dose (1 x 200 mg/30 mg liquid filled soft gel capsule) of Cold & Sinus Relief Capsules [ibuprofen (free acid and potassium salt)/ pseudoephedrine hydrochloride] 200 mg/30 mg liquid filled soft gel capsules (Apotex Inc.) and Advil® Cold & Sinus Liqui-Gel® [ibuprofen (free acid and potassium salt)/ pseudoephedrine hydrochloride] 200 mg/30 mg capsules (Wyeth Consumer Healthcare Inc., Canada).

Summary Table of the Comparative Bioavailability Data Ibuprofen (A single 200 mg/30 mg dose: 1 x 200 mg/30 mg) From Measured Data/Fasting Conditions Geometric LS Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric LS Means (%)	90% Confidence Interval (%)
AUC_T (mcg·h/mL)	66.22 67.02 (15.55)	64.71 65.09 (12.54)	102.34	98.18 - 106.68
AUC_∞ (mc□g·h/mL)	68.99 69.85 (15.78)	67.53 67.91 (12.57)	102.15	97.81- 106.67
C_{max} (mcg/mL)	23.85 24.86 (27.88)	22.24 23.18 (23.51)	107.25	95.90 - 119.95
T_{max}§ (h)	0.75 (0.25 – 2.00)	0.71 (0.33 – 2.00)		
$T_{½}$€ (h)	2.17 (12.82)	2.21 (16.85)		

* Cold & Sinus Relief Capsules [ibuprofen (free acid and potassium salt)/ pseudoephedrine hydrochloride] 200 mg/30 mg liquid filled soft gel capsules (Apotex Inc.)
† Advil® Cold & Sinus Liqui-Gel® [ibuprofen (free acid and potassium salt)/ pseudoephedrine hydrochloride] 200 mg/30 mg capsules (Wyeth Consumer Healthcare Inc., Canada) was purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Summary Table of the Comparative Bioavailability Data Pseudoephedrine (A single 200 mg/30 mg dose: 1 x 200 mg/30 mg) From Measured Data/Fasting Conditions Geometric LS Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric LS Means (%)	90% Confidence Interval (%)
AUC_T (ng·h/mL)	1052.38 1092.98 (27.28)	1051.26 1090.47 (28.53)	100.11	92.82 – 107.97
AUC_∞(ng·h/mL)	1093.80 1140.18 (28.74)	1090.63 1136.28 (31.00)	100.29	92.80 – 108.39
C_{max} (ng/mL)	109.76 113.13 (22.18)	107.93 111.71 (25.96)	101.69	96.15 – 107.55
T_{max}§ (h)	1.75 (0.75 – 3.00)	1.52 (0.75 – 4.00)		
$T_{½}$€ (h)	6.99 (27.57)	6.56 (25.81)		

* Cold & Sinus Relief Capsules [ibuprofen (free acid and potassium salt)/ pseudoephedrine hydrochloride] 200 mg/30 mg liquid filled soft gel capsules (Apotex Inc.)
† Advil® Cold & Sinus Liqui-Gel® [ibuprofen (free acid and potassium salt)/ pseudoephedrine hydrochloride] 200 mg/30 mg capsules (Wyeth Consumer Healthcare Inc., Canada) was purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV%) only

Study results
Published studies have documented the efficacy of 200-mg and 400-mg doses of ibuprofen in treating mild to moderate pain, including sore throat pain [37], headache [38, 39], and muscle aches [40] in adults. The antipyretic efficacy of ibuprofen has been demonstrated in adults at doses of 200 and 400 mg [41, 42, 43] and in children at doses of 5 to 10 mg/kg [44, 45, 158, 46, 47, 48, 49]. Ibuprofen is effective in treating the pain of sore throat in children [50, 51, 52]

A randomized, double-blind, placebo-controlled study in 179 subjects with nasal congestion secondary to upper respiratory tract infection showed a statistically significant increase in total nasal airflow 2 hours after single oral doses of pseudoephedrine 60 mg or ibuprofen 400 mg plus pseudoephedrine 60 mg [159]. Time-weighted sums of changes in nasal airflow relative to baseline were greater with both active treatments than with placebo (Table 5).

Table 5 Mean Nasal Air Flow (Standard Deviation) after Single Doses of Pseudoephedrine 60 mg or Ibuprofen 400 mg plus Pseudoephedrine 60 mg in Subjects with Upper Respiratory Infection

		Mean Nasal Air Flow Rate (mL/sec)		P Value versus Placebo[a]	
Treatment	**N**	**First 4 Hours Postdose**	**Entire 6-Hour Period Postdose**	**First 4 Hours Postdose**	**Entire 6-Hour Period Postdose**
Placebo	58	106 (362)	194 (569)	---	---
Pseudoephedrine 60 mg	61	247 (387)	406 (580)	0.068	0.061
Ibuprofen 400 mg + pseudoephedrine 60 mg	60	266 (481)	412 (639)	0.015	0.021

[a] Pairwise comparisons. Additional pairwise comparisons showed no significant differences between the two active treatments (p = 0.524 for the first 4 hours postdose, 0.653 for the entire 6-hour period postdose).

Pseudoephedrine at a dose of 60 mg increases maximal nasal inspiratory flow rate [160] and produces objective improvement in nasal airway resistance [54]. A single 60-mg oral dose of pseudoephedrine produced marked nasal decongestant effects within 30 minutes of administration, lasting for at least 4 hours [55]. In 40 subjects with nasal congestion associated with the common cold, two 60-mg doses of pseudoephedrine 4 hours apart produced no significant difference in maximum unilateral nasal airflow or total nasal air flow over a 7-hour period; however, minimum unilateral nasal air flow was significantly increased [56]. A single 60-mg dose of pseudoephedrine administered to subjects with nasal congestion due to the common cold significantly increased total

nasal minimum cross-sectional area and nasal volume measured by acoustic rhinometry [57]. There was no significant change in nasal area as measured by active posterior rhinomanometry [57].

In a double-blind, randomized study conducted by Pfizer Consumer Healthcare [161], the decongestant activity of pseudoephedrine was dose related over the range of 30 to 60 mg, as measured by total nasal air flow (sum of left and right nares) in 112 subjects with nasal congestion associated with allergic rhinitis (Figure 1). At most time points postdose, the decongestant effect of the combination of ibuprofen 200 mg plus pseudoephedrine 30 mg was midway between that seen for pseudoephedrine 45 mg and 60 mg and greater than the decongestant effect of pseudoephedrine 30 mg (Table 6).

Figure 1. Mean Change in Nasal Air Flow after Single Oral Doses of Pseudoephedrine in Subjects with Allergic Rhinitis [62]

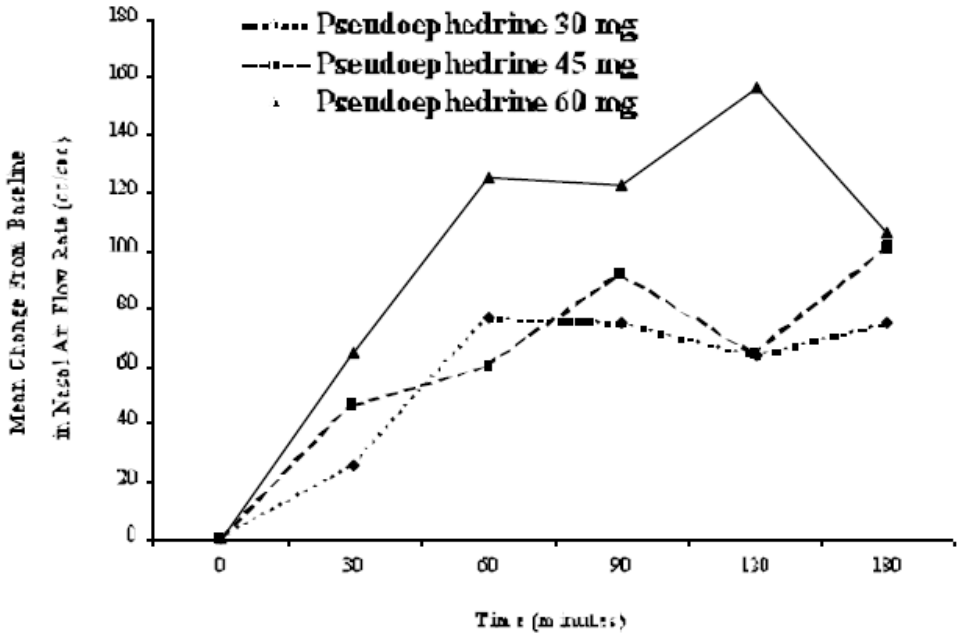


Table 6 Mean Nasal Air Flow (Standard Deviation) after Single Doses of Pseudoephedrine (30, 45, or 60 mg) or Ibuprofen 200 mg plus Pseudoephedrine 30 mg in Subjects with Allergic Rhinitis

Treatment	N	Mean Nasal Air Flow (mL/sec) at Specified Time Postdose, in Minutes						
		-30 Min	0 Min	30 Min	60 Min	90 Min	120 Min	180 Min
Pseudoephedrine								
30 mg	28	440 (185)	365 (101)	394 (152)	442 (174)	440 (173)	429 (158)	440 (155)
45 mg	28	406 (153)	356 (134)	401 (138)	416 (146)	450 (169)	423 (159)	457 (182)
60 mg	28	422	328	393	454	451	485	435

		(143)	(119)	(157)	(217)	(196)	(214)	(136)
Ibuprofen 200 mg + pseudoephedrine 30 mg	28	416 (147)	365 (143)	416 (196)	454 (173)	429 (154)	468 (177)	477 (201)

Note: Time 0 = time of administration of study medication. Min = minutes.

DETAILED PHARMACOLOGY

Ibuprofen

Animal Pharmacology

Cyclooxygenase inhibitors such as ibuprofen and other NSAIDs reduce thromboxane A_2 production and release, thereby decreasing platelet aggregation [117]. Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated in vivo by prevention of platelet disposition in aortopulmonary arterial bypass grafts in dogs [118]. The drug's protective action against pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to inhibition of platelet aggregation [119, 120]. The decreased platelet aggregation may be due in part to a reduction in membrane fluidity [121].

The penetration of ibuprofen into rabbit and rat foetuses was investigated. Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C^{14}-labeled ibuprofen [11]. Rabbits were killed 3 hours after dosing, and rats were killed 1.5 hours after dosing. Blood samples were collected from the mothers and foetuses. The concentrations of radioactively labelled material were similar in maternal and foetal blood, indicating that ibuprofen and its metabolites readily crossed the placenta and entered the foetal circulation.

In healthy volunteers, platelet aggregation decreased significantly at a dosage of 1800 mg per day of ibuprofen given over a period of 28 days. Ibuprofen influenced ADP-induced aggregation to a lesser extent than collagen-induced aggregation. 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 measured 2 hours after administration of ibuprofen showed a significant, dose-related increase.

Pseudoephedrine Hydrochloride

Animal Pharmacology

In dogs, pseudoephedrine acts as a vasopressor and vasoconstrictor with positive inotropic and chronotropic effects. In all these effects, pseudoephedrine is less potent than ephedrine [122]. The bronchodilating potencies of pseudoephedrine and ephedrine in anaesthetized dogs are approximately equal [123], but pseudoephedrine produces a greater degree of nasal decongestion with less cardiovascular involvement than ephedrine [124]. Pseudoephedrine increases plasma corticosterone levels and produces hyperglycemia in mice [125].

Human Pharmacology

Pseudoephedrine at doses up to 180 mg is approximately one-fourth as potent as ephedrine in producing tachycardia and increased systolic blood pressure; diastolic pressure is unchanged [126]. After a single dose of pseudoephedrine 180 mg immediate release, three divided doses of 60 mg, or a

sustained-release 180-mg dose, increases in heart rate and diastolic blood pressure were noted [29]. At doses from 60 mg to 240 mg, few changes in pulse rate were noted, and no abnormalities or ectopic beats were noted on an electrocardiogram; at 210 mg, changes in diastolic blood pressure were noted [127].

Single pseudoephedrine doses of 180 mg produced minor elevations in systolic blood pressure (about 7 mmHg), minor increases in heart rate (about 9 beats per minute), and no changes in diastolic blood pressure in healthy subjects [128]. Single doses of 60 mg had minimal effects.

Clinical studies of the cardiovascular effects of pseudoephedrine in subjects with controlled hypertension have produced differing results. A single 60-mg dose of pseudoephedrine compared with placebo produced significant increases in mean systolic blood pressure and heart rate in 20 hypertensive subjects [129]. Mean diastolic blood pressure and mean arterial pressure also increased, but not significantly. Beck et al found minimal increases in blood pressure and heart rate in patients with medically controlled hypertension treated with 120 mg sustained-release pseudoephedrine twice daily [130]. In other studies, pseudoephedrine at standard doses had no significant effect on systolic or diastolic blood pressure [131, 132]. In subjects with phaeochromocytoma, pseudoephedrine increased blood pressure and plasma noradrenaline concentration [133].

In children 6 to 12 years of age given 30-mg and 60-mg doses of pseudoephedrine in a pharmacokinetic study, pulse rate increased significantly at 4 hours postdose, particularly after the 60 mg dose [159, 33]. No clinically important adverse effects on blood pressure or on the central nervous system were noted.

A dose-related increase in frequency of sinus arrhythmias was observed after treadmill exercise in healthy subjects receiving pseudoephedrine [134]. The mean number of episodes of arrhythmia during recovery from exercise was 0.17, 2.17, and 4.33 in subjects pretreated with placebo, pseudoephedrine 60 mg, and pseudoephedrine 120 mg, respectively. Short-lived unifocal premature ventricular contractions were experienced by two subjects.

In an investigation of the effects on pseudoephedrine on uterine and foetal blood flow, 12 healthy, pregnant women between 26 and 40 weeks of gestation ingested a 60-mg dose of pseudoephedrine [135]. Doppler blood flow measurements taken during the first 3 hours after drug ingestion showed no significant alterations in maternal or foetal circulation.

Pseudoephedrine at a dose of 180 mg was reported to produce no significant mood alterations or changes in subjective ratings of mental state [27, 127]. In a study of the effects of pseudoephedrine on day- and night time central nervous system activity, there was no evidence of impairment of daytime activity as measured by objective tests (critical flicker fusion, choice reaction time, simulated car tracking test, and Sternberg Memory Scanning Test) or subjective tests (analog rating scales) [136]. Improvements were seen in psychomotor function (choice reaction time) and information processing (critical flicker fusion). Detrimental effects on night time central nervous system activity indicative of sleep disturbances (electroencephalogram, Leeds Sleep Evaluation Questionnaire) were noted with pseudoephedrine at doses of 60 mg and 120 mg [137].

Pseudoephedrine administered as a single 60-mg dose [135, 137] or 120-mg dose [135, 138] or administered at 1 to 2 mg/kg [139] had no significant effect on exercise performance. Pseudoephedrine at doses of 60 mg and 120 mg had no effect on the time required to reach 85% maximal predicted heart rate on a treadmill or to return to baseline heart rate; on blood pressure at

rest, during exercise, or in the recovery period; or on post-exercise blood glucose and insulin levels [135].

The effect of pseudoephedrine as a bronchodilator is small at a 210-mg dose and is approximately one-half that of ephedrine [128]. In a study of subjects with reversible airway obstruction, pseudoephedrine at 60 mg and 180 mg produced no significant bronchodilation [140].

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Ibuprofen

Single-dose toxicity studies have been conducted in mice, rats, and dogs [11]. The LD_{50} values for ibuprofen in mice and rats, expressed as mg/kg of body weight, are as follows:

Mice	Oral	800 mg/kg
	Intraperitoneal	320 mg/kg
Rats	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. Single ibuprofen doses of 125 mg/kg and above in dogs caused emesis, transient albuminuria, faecal blood loss, and erosions in the gastric antrum and pylorus. No ill effects were seen with doses of 20 or 50 mg/kg.

The primary toxic effect of ibuprofen in repeated doses in rats is intestinal damage [11]. At a dosage of 180 mg/kg/day for 26 weeks, ibuprofen alters the organ-to-body weight ratio of certain organs, such as the liver, kidneys, gonads, and secondary sex organs, although no histological abnormalities have been observed and the effects are 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 effects on other organs is unknown. When administered in lethal doses (540 mg/kg/day), ibuprofen produces mild kidney lesions in addition to intestinal damage.

In rats 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 [141]. There was no evidence of tumour induction, indicating that ibuprofen is not carcinogenic in rats. Ibuprofen is not teratogenic when given in toxic doses (60 mg/kg/day) to rabbits or in ulcerogenic doses (180 mg/kg/day to rats [11].

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 fetal 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 cyclopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits.[11]

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.[11]

Penetration of Ibuprofen into the Rabbit and Rat Fetus
Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C14 labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and fetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and fetus indicating that the drug and its metabolites readily crossed the placental barrier into the fetal circulation.[11]

Pseudoephedrine Hydrochloride
Mice injected with toxic doses of pseudoephedrine manifest increased motor activity, piloerection, and mydriasis, and they eventually die in respiratory exhaustion. The intravenous LD_{50} in mice is approximately 90 mg/kg [123]. The approximate oral LD_{50} values are 726 mg/kg (mice), 2206 mg/kg (rats), 1117 mg/kg (rabbits), 105 mg/kg (beagle dogs), and 307 mg/kg (mongrel dogs). Toxic effects of pseudoephedrine include increased respiratory activity, salivation, and lacrimation; loss of pupillary reflex in reaction to light; tremor, convulsions, and cardiac arrhythmias [142].

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

Mice	Oral	726
	Intravenous	90
Rats	Oral	2206
Rabbits	Oral	1117
Dogs, beagle	Oral	105
Dogs, mongrel	Oral	307

REFERENCES

1) Insel, PA. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In Molinoff PB, Ruddon RW, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill, 1996: 617-657.

2) Nozu K: Flurbiprofen: Highly potent inhibitor of prostaglandin synthesis. Biochim Biophys Acta 1978; 529: 493-496.

3) Moncada S, Vane JR: Mode of action of aspirin-like drugs. Intern Med 1979; 24: 1-22.

4) Adams SS, Buckler JW: Ibuprofen and flurbiprofen. Clinics Rheum Dis 1979; 5: 359-379.

5) Rudy AC, Knight PM, Brater DG, Hall SD: Enantioselective disposition of ibuprofen in elderly persons with and without renal impairment. J Pharmacol Exp Ther 1995; 273: 88-93.

6) Brown RD, Wilson JT, Kearns GL, Eichler VF, Johnson VA, Bertrand KM: Single-dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. J Clin Pharmacol 1992; 32: 231-241.

7) Nahata MC, Durrell DE, Powell DA, Gupta N: Pharmacokinetics of ibuprofen in febrile children. Eur J Clin Pharmacol 1991; 40: 427-428.

8) Walson PD, Galletta G, Braden NF, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin Pharmacol Ther 1989;46:9-17.

9) Davies NM: Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin Pharmacokinet 1998;34:101-154.

10) Dollery C: Ibuprofen. In Therapeutic Drugs, 1st ed, Churchill Livingston, 11-14. 1991.

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

12) Mills RFN, Adams SS, Cliffe EE, et al: The metabolism of ibuprofen. Xenobiotica 1973; 3(9):589.

13) Leeman TD, Tanson C, Bonnabry C, Dayer P: A major role for cytochrome P450 TB (CYP2C subfamily) in the actions of non-steroidal anti-inflammatory drugs. Drugs Exp Clin Res 1993; 19: 189-195.

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

15) Walter K, Dilger C: Ibuprofen in human milk. Br J Pharmacol 1997; 44: 211-212.

16) Sympathomimetic (Adrenergic) Agents. In McEvoy GK, editor. Bethesda, Maryland: American Society of Health-System Pharmacists, American Hospital Formulary Service Drug Information, 1999: 1088-1156.

17) Kanfer I, Dowse R, Vuma V. Pharmacokinetics of oral decongestants. Pharmacotherapy 1993;13:116S-128S.

18) Graves DA, Rotenberg KS, Woodworth JR, Amsel LP, Hinsvark ON. Bioavalability assessment of a new liquid controlled-release pseudoephedrine product. Clin Pharm 1985;4:199-203.

19) Graves DA, Woodworth JR, Hinsvark ON, Rotenberg KS. Single- and multiple-dose bioavailability studies for a controlled-release pseudoephedrine capsule formulation. Curr Ther Res 1988;43:630-635.

20) WeckerMT, Graves DA, Amsel LP, Hinsvark ON, Rotenburg KS. Influence of a standard meal on the absorption of controlled-release pseudoephedrine capsules. J Pharm Sci 1987;76:29-31.

21) Autritt WA, Saccar CL, HandfingerMG, Mansmann HC, Yaffe SJ, Warren JT, Welch RM, Findlay JWA. Pharmacokinetics of pseudoephedrine in children (abstract). Ann Allergy 1981;47:PI39.

22) Whitehall-Robins Healthcare. Clinical Study AQ-99-01. A single-dose, randomized, open-label, single center, two-way crossover pharmacokinetic study of Advil Cold & Sinus tablets in children; 1999.

23) Lucarotti RL, Colaizzi JL, Barry H III, Poust RI. Enhanced pseudoephedrine absorption by concurrent administration of aluminum hydroxide gel in humans. J Pharm Sci 1972;61:903-905.

24) Williams BO, Liao SH, Lai AA, Arnold JP, Perkins JG, Blum MR, Findlay JW. Bioavailability of pseudoephedrine and triprolidine from combination and single ingredient products. Clin Pharm 1984;3:638-643.

25) Dickerson J, Perrier D, Mayerson M, Bressler R. Dose tolerance and pharmacokinetic studies of L(+) pseudoephedrine capsules in man. Eur J Clin Pharmacol1978;14:253-259.

26) Baaske DM, Lai CM, Klein L, Look ZM, Yacobi A. Comparison of GLC and high pressure liquid chromatographic methods for analysis of urinary pseudoephedrine. J Pharm Sci 1979;68:1472.

27) Bye C, Hill HM, Hughes Dill, Peck AW. A comparison of plasma levels of L(+) pseudoephedrine following different formulations, and their relation to cardiovascular and subjective effects in man. Eur J Clin Pharmacol1975;8:47-53.

28) Delbeke FT, Debackere M. The influence of diuretics on the excretion and metabolism of adoping agents. VI. Pseudoephedrine. Biopharm Drug Dispos 1991;12:37-48.

29) Lai CM, Stoll RG, Look ZM, Yacobi A. Urinary excretion of chlorpheniramine and pseudoephedrine in humans. J Pharm Sci 1979;68:1243-1246.

30) Lo L Y, Land G, Bye A. Sensitive assay for pseudoephedrine and its metabolite, norpseudoephedrine in plasma and urine using gas-liquid chromatography with electroncapture detection. J Chromatogr Biomed Appl 1981;222:297-302.

31) Brater DC, Kaojaren S, Benet LZ, Lin ET, Lockwood T, Morris RC, McSherry EJ, Melmond KL. Renal excretion of pseudoephedrine. Clin Pharmacol Ther 1980;28:690-694.

32) Kuntzman RG, Tsai I, Brand L, Mark LC. The influence of urinary pH on the plasma half- life of pseudoephedrine in man and dog and a sensitive assay for its determination in human plasma. Clin Pharmacol Ther 1971;12:62-67.

33) Gu X, Simons KJ, St. Vincent JCM, Watson WTA, Reggin ill, Simons FER. Pseudoephedrine (PDE) pharmacokinetics and pharmacodynamics in children with allergic rhinitis (abstract). J Allergy Clin Immunol1996;97:199.

34) American Hospital Formulary Service Drug Evaluation -Pseudoephedrine. McEvoy GK, editor. Bethesda, MD: American Society of Health-System Pharmacists; 1998:1064-1066. 37. Findlay JWA, Butz RF, Sailstad JM, Warren JT, Welch RM. Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. Br J Clin Pharmacol 1984;18:901-906.

35) Findlay JWA, Butz RF, Sailstad JM, Warren JT, Welch RM. Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. Br J Clin Pharmacol 1984;18:901-906.

36) Mortimer EA: Drug toxicity from breast milk? Pediatrics 1977; 60:780-781.

37) Schachtel BP, Fillingim lM, Thoden WR, Lane AC, Baybutt RI: Sore throat pain in the evaluation of mild analgesics. Clin Pharmacol Ther 1988; 44: 704-711.

38) Schachtel BP, Furey SA, Thoden WR: Nonprescription ibuprofen and acetaminophen in the treatment of tension-type headache. J Clin Pharmacol1996; 36: 1120-1125.

39) Schachtel BP, Thoden WR: Onset of action of ibuprofen in the treatment of muscle contraction headache. Headache 1988; 28: 471-474.

40) Braun RP, Lockhart EA, Bruno P: Delayed-onset muscle soreness (DOMS)- a new pain model to compare OTC analgesics. Med Sci Sports Exer 1994; 26: S14.

41) Minor MG, Schachtel BP: Antipyretic efficacy of ibuprofen 200 mg in adults with acute upper respiratory tract infection (URI). J Clin Pharmacol1990; 30: 846.

42) Jain AK, Vargas R, McMahon FG: The antipyretic effect of over-the-counter dosages of aspirin, acetaminophen and ibuprofen in endotoxin-induced fever. Clin Pharmacol Ther 1993; 53: 153.

43) Thoden WR, Lockhart EA: Antipyretic efficacy of ibuprofen and naproxen in flu-like upper respiratory illness. J Clin Pharmacol1995; 35: 929.

44) Nahata MC, Powell DA, Durrell DE, Miller MA: Efficacy of ibuprofen in pediatric patients with fever. Int J Clin Pharmacol Ther Toxicol 1996; 30: 94-96.

45) Aksoylar S, Aksit S, Caglayan S, Yaprak I, Bakiler R, Cetin F: Evaluation of sponge and antipyretic medication to reduce body temperature in febrile children. Acta Paediatr 1997; 39: 215-217.

46) Autret E, Reboul-Marty J, Henry-Launois B, Laborde C, Courcier S, Goehrs JM, Languilat G, Launois R: Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever. Eur J Clin Pharmacol1997; 51: 367-371.

47) Khubchandani RP, Ghatikar KN, Keny S, Usgaonkar NGS: Choice of antipyretic in children. J Assoc Physicians India 1995; 43: 614-616.

48) McIntyre J, Hull D: Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. Arch Dis Child 1996; 74: 164-167.

49) Vauzelle-Kervroedan F, d' Athis P, Pariente-Khayat A, Debregeas S, Olive G, Pons G: Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children. J Pediatr 1997; 131: 683-687.

50) Lockhart EA, Thoden WR, Furey SA, Schachtel BP: Ibuprofen and streptococcal sore throat pain in children. Clin Pharmacol Ther 1993; 53: 147.

51) Schachtel BP, King SA, Thoden WR: Pain relief in children; A placebo-controlled model. Clin Pharmacol Ther 1991; 49: 154.

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

53) Data on File. A placebo-controlled comparison of the nasal decongestant effect of the combination of ibuprofen 400 mg with pseudoephedrine 60 mg to pseudoephedrine 60mg on nasal airway resistance in patients with acute upper respiratory tract infection. Whitehall-Robins Healthcare Clinical Study WM-389; 1991.

54) Cho YW. A new passive anterior rhinometric method for clinical study of nasal decongestant. Int J Clin Pharmacol 1978;16:63-67.

55) Roth RP, Cantekin EI, Bluestone CD, Welch RM, Cho YW. Nasal decongestant activity of pseudoephedrine. Ann Otol1977;86:235-242.

56) Jawad SS, Ecces R. Effect of pseudoephedrine on nasal airflow in patients with nasal congestion associated with common cold. Rhinology 1998;36:73-76.

57) Taverner D, Dang C, Economos D. The effects of oral pseudoephedrine on nasal patency in the common cold: a double-blind single-dose placebo-controlled trial. Clin Otolaryngol 1999;24:47-51.

58) Data on File. A single-dose, double-blind, parallel, randomized, controlled study of nasalairflow rates in patients with nasal congestion treated with ibuprofen 200 mg andpseudoephedrine 30 mg compared with pseudoephedrine 30 mg, 45 mg, or 60 mg.Whitehall-Robins Healthcare Clinical Study WM-315A; 1987.

59) Drugdex, Pseudoephedrine Drugdex Drug Evaluations: MICROMEDEX, 2002.

60) Dowd J, Bailey D, Moussa K, Nair et al: Ischemic colitis associated with pseudoephedrine: four cases. Am J Gastroenterol1999; 94(9):2430-2434.

61) Buchanan BJ, Hoagland J, Fischer PR: Pseudoephedrine and air travel-associated ear pain in children. Arch Pediatr Adolesc Med 1999; 153:466-468.

62) Billings CE, Ralston RH, Hare DE: Untoward effects of a sympathomimetic amine. Aerosp Med 1974; 45(5):551-552.

63) Whelton A, Hamilton CW: Nonsteroidal anti-inflammatory drugs: Effects of kidney function. J Clin Pharmacol 1991; 588-598.

64) Novack SN: Side effect of ibuprofen therapy (letter). Arthritis Rheum 1973; 18(6):628.

65) Sica DA, Comstock TJ: Pseudoephedrine accumulation in renal failure. Am J Med Sci 1989; 298(4):261-263.

66) Nicastro NJ: Visual disturbances associated with over-the-counter ibuprofen in three patients. Ann Ophthalmol 1989; 29:447-450.

67) Collum LMT, Bowen DI: Ocular side-effects of ibuprofen. Br J Ophthalmol 1971; 55(7):472-477.

68) Palmer CA: Toxic amblyopia from ibuprofen. Br Med J 1972; 3(829):765.

69) Asherov J, Schoenberg A, Weinberger A: Diplopia following ibuprofen administration (letter). JAMA 1982; 248(6):649.

70) Pugh CR, Howie SM: Dependence on pseudoephedrine (letter). Br J Psychiatry 1986; 149:798.

71) Diaz MA, Wise TN, Semchyshyn GO: Self-medication with pseudoephedrine in a chronically depressed patient. Am J Psychiatry 1979; 136(9):1217-1218.

72) Penner JA, Abbrecht PH: Lack of interaction between ibuprofen and warfarin. Cuff Ther Res 1975;18:862-871.

73) Slattery JT, Levy G: Effect of ibuprofen on protein binding of warfarin in human serum. J Pharm Sci 1977-66:1060.

74) Nierenberg DW: Competitive inhibition of methotrexate accumulation in rabbit kidney slices by non-steroidal anti-inflammatory drugs. J Pharmacol Exper Ther 1983;226(1):1-6.

75) Ragheb M, Alvin C: Ibuprofen can increase serum lithium in lithium treated patients. J Clin Psychiatry 1987; 48: 161-163.

76) Mork NL, Robertson RP: Effects of nonsteroidal antiinflammatory drugs in conventional dosage on glucose homeostatis in patients with diabetes. West J Med 1983; 139:45-49.

77) Gontarz N, Small RE, Comstock TJ, Stalker DJ, Johnson SM, Willis BE: Effects of antacid suspension on the pharmacokinetics of ibuprofen. Clin Pharm 1987; 7(5):413-416.

78) Furey SA, Thoden WR, Greene JJ, Schachtel BP: Side effect profile of ibuprofen with pseudoephedrine in upper respiratory tract infection. J Clin Pharmacol1996; 36(9):857.

79) Sperber SJ, Sorrentino JV, Riker DK, Hayden FG: Evaluation of an alpha agonist alone and in combination with a nonsteroidal antiinflammatory agent in the treatment of experimental rhinovirus colds. Bull NY Acad Med 1989; 65(1): 145-160.

80) Doyle G, Furey S, Berlin R, Cooper S, Jayawardena S, AshrafE, Baird L: Gastrointestinal safety and tolerance of ibuprofen maximum over-the-counter use. Aliment Pharmacol Ther 1999; 13: 897-906.

81) Furey SA, Waksman JA, Dash BH: Nonprescription ibuprofen: side effect profile. Pharmacotherapy 1992; 12: 403-407.

82) DeArmond B, Francisco CA, Lin JS, Huang FY, Halladay S, Bartizek RD, Skare KL: Safety profile of over- the-counter naproxen sodium. Clin Therap 1995; 17: 587-601.

83) Kellstein DE, Waksman JA, Binstok G, Furey SA, Cooper SA: The safety profile of nonprescription ibuprofen in multiple-dose use: a meta-analysis. J Clin Pharmacol 1999;39: 520-532.

84) Rainsford KD, Roberts SC, Brown S: Ibuprofen and paracetamol: relative safety in nonprescription dosages. J Pharm Pharmacol 1997; 49: 345-376.

85) Rainsford KD, Quadir M: Gastrointestinal damage and bleeding from non-steroidal anti inflammatory drugs. I. Clinical and epidemiological aspects. Inflammopharmacology 1995; 3: 169-190.

86) Strom BL: Gastrointestinal tract bleeding associated with naproxen sodium vs ibuprofen. Arch Intern Med 1997; 157: 2636-2631.

87) Gutthann SA, Garcia-Rodriguez LA, Duque-Oliart A, Varas-Lorenzo C: Low-dose diclofenac, naproxen, and ibuprofen cohort study. Pharmacoepidemiology 199; 19: 854- 859.

88) Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Herschel J: Acute liver injury associated with non- steroidal anti-inflammatory drugs and the role of risk factors. Arch Intern Med 1994; 154: 311-316.

89) Lesko SM, Mitchell AA: An assessment of the safety of pediatric ibuprofen. 1995; 273(12): 929-933.

90) Lesko SM, Mitchell AA: Renal function after short-term ibuprofen use in infants and children. Pediatrics 1997; 100: 954-957.

91) Lesko SM, Mitchell AA: The safety of acetaminophen and ibuprofen among children less than two years old. Pediatrics 1999 104 (4): 39-49.

92) Franklin QJ: Sudden death after typhoid and Japanese encephalitis vaccination in a young male taking pseudoephedrine. Mil Med 1999;164(2):157-159.

93) Rutstein HR: Ingestion of pseudoephedrine. Arch Otolaryngol1963; 77:145-147.

94) Beary IF, 3rd: Pseudoephedrine producing postural hypotension in a pilot. Aviat Space Environ Med 1977; 48(4):369.

95) Wiener I, Tilkian AG, Palazzolo M: Coronary artery spasm and myocardial infarction in a patient with normal coronary arteries: temporal relationship to pseudoephedrine ingestion. Cathet Cardiovasc Diagn 1990;20(1):51-53.

96) Brownstein MH: Fixed eruptions due to an ephedrine isomer. Arch Dermatol 1968; 97(2):115-119.

97) Carnisa C: Fixed drug eruption due to pseudoephedrine. Cutis 1988; 41(5):339-340.

98) Shelley WB, Shelley ED: Nonpigmenting fixed drug eruption as a distinctive reaction pattern: examples caused by sensitivity to pseudoephedrine hydrochloride and tetrabydrozoline. JAm Acad Dermatol 1987; 17(3):403-407.

99) Hauken M: Fixed drug eruption and pseudoephedrine (letter). Ann Intern Med 1994; 120:442.

100) Hindioglu U, Sabin S: Nonpigmenting solitary fixed drug eruption caused by pseudoephedrine hydrochloride. JAm Acad Dermatol 1999; 38(3): 499-500.

101) Taylor BJ, Duffill MB: Recurrent pseudo-scarlatina and allergy to pseudoephedrine hydrochloride. Br J Dermatol 1988; 118(6):827-829.

102) Cavanah DK, Ballas ZK: Pseudoephedrine reaction presenting as recurrent toxic shock syndrome. Ann Intern Med 1993; 119:302-303.

103) Mattana J, Perinbasekar S, Brod-Miller C: Am J Med Sci 1997; 313:117-119.

104) Kim J, Gazarian M, Verjee Z, Johnson D: Acute renal insufficiency in ibuprofen overdose. Ped Emerg Care 1995; 11(2): 107-108.

105) Al-Harbi NN, Domrongkitchaipom S, Lireman DS: Hypocalcemia and hypomagnesemia after ibuprofen overdose. Ann Pharmacother 1997; 31: 432-434.

106) Zuckerman GB, Uy CC: Shock, metabolic acidosis, and coma following ibuprofen overdose in a child. Ann Pharmacother 1995; 29(9): 869-871.

107) Mariani PJ: Pseudoephedrine-induced hypertensive emergency: treatment with labetalol. Am J Emerg Med 1986; 4(2):141-142.

108) Wezorek C, Dean B, Krenzelok E: Pseudoephedrine: a prospective study to establish a toxic dose in children. Clin Toxicol 1995; 33(5): 554.

109) Saken R, Kates GL, Miller K: Drug-induced hypertension in infancy. J Pediatr 1979; 95(6):1077-1079.

110) Roberge RJ, Hirani KH, Rowland PL, Berkeley R, Krenzelok EP: Dextromethorphan- and pseudoephedrine- induced agitated psychosis and ataxia: case report. J Emerg Med 1999; 17(2): 285-288.

111) Sauder KL, Brady WJ Jr, Hennes H: Visual hallucinations in a toddler: Accidental ingestion of a sympathomimetic over-the-counter nasal decongestant. Am J Emerg Med 1997; 15(5): 521-526.

112) Ackland PM: Hallucinations in a child after drinking triprolidine/pseudoephedrine linctus. Lancet 1984; 1(8387):1180.

113) Leighton KM: Paranoid psychosis after abuse of Actifed. Br Med J (Clin Res Ed) 1982; 284(6318):789-790.

114) Dalton R: Mixed bipolar disorder precipitated by pseudoephedrine hydrochloride. South Med J 1990; 83(1):64-65.

115) Clark RF, Curry SC: Pseudoephedrine dangers. Pediatrics 1990; 85(3):389-390.

116) Post-marketing surveillance Product Safety Update Report, 2001, Whitehall-Robins Healthcare.

117) Utsunomiya T, Krausz MM, Dunham B, Valeri CR, Levine L, Shepro D, Hechtman HB: Modification of inflammatory response to aspiration with ibuprofen. Am J Physiol 1982; 243: H903-910.

118) Lillehei TJ, Metke MP, Dawnajee MK, Tago M, Lim MF, Kaye MP: Reduction of platelet deposition in aorto-coronary artery Gore- Tex bypass grafts in dogs by platelet inhibitors. Circulation 1980; 62: Suppl3; 53.

119) Dipasquale G, Mellace D: Inhibition of arachidonic acid induced mortality in rabbits with several non- steroidal anti-inflammatory agents. Agents Actions 1977; 7: 481-485.

120) Adesuyi SA, Ellis EF: The effect of ibuprofen dose on rabbit platelet aggregation and aortic PGI2 synthesis. Thromb Res 1982; 28: 581-585.

121) Imai H, Muramatsu Y, Tsurumi K, Fujimura H: Platelet aggregation and liposome as a model system (abstract). Jap J Pharmacol 1981; 31: 92P.

122) Patil PN, Tye A, LaPidus JB: A pharmacological study of the ephedrine isomers. J Pharmacol Exp Ther 1965; 148:158-168.

123) Aviado DM, Wnuck AL, De Beer EJ. Cardiovascular effects of sympathomimetic bronchodilators: epinephrine, ephedrine, pseudoephedrine, isoproterenol, methoxyphenarnine, and isoprophenamine. J Pharmacol Exp Ther 1958;122:406-417.

124) Aviado DM, Wnuck AL, De Beer ES. A comparative study of nasal decongestion by sympathomimetic drugs. Arch Otolaryngol 1959;69:589-605.

125) Sandago BW, Fletcher HP. Glycemic response to selected sympathomimetics in stressed and normal goldthioglucose mice. Pharmacology 1983;27:110-116.

126) Bye C, Dewsbury D, Peck A W. Effects on the human central nervous system of two isomers of ephedrine and triprolidine, and their interaction. Br J Clin Pharmacol 1974;1:71-78.

127) Drew CDM, Knight GT, Hughes DTD, Bush M. Comparison of the effects ofD(-) ephedrine and L-(+)- pseudoephedrine on the cardiovascular and respiratory systems in man. Br J Clin Pharmacol 1978;6:221-225.

128) Empey DW, Young GA, Letley E, John GC, Smith P, McDonnell KA, et al: Dose-response study of the nasal decongestant and cardiovascular effects of pseudoephedrine. Br J Clin Pharmacol 1980; 9(4):351-358.

129) Chua SS, Benrimoj SI, Gordon RD, Williams G: A controlled clinical trial on the cardiovascular effects of single doses of pseudoephedrine in hypertensive patients. Br J Clin Pharmacol 1989; 28(3):369-372.

130) Beck RA, Mercado DL, Seguin SM, Andrade WP, Cushner HM. Cardiovascular effects of pseudoephedrine in medically controlled hypertensive patients. Arch Intern Med 1992;152:1242-1245.

131) Bradley JG, Kallail KJ, Dorsch IN, Fox J. The effects of pseudoephedrine on blood pressure in patients with controlled, uncomplicated hypertension: a randomized, double-blind, placebo-controlled trial. J Am Board Fam Pract 1991;4:201-206.

132) Coates ML, Rembold CM, Farr BM. Does pseudoephedrine increase blood pressure in patients with controlled hypertension? J Fam Pract 1995;40:22-26.

133) Gordon RD, Ballantine DM, Bachmann A W. Effects of repeated doses of pseudoephedrine on blood pressure and plasma catecholamines in normal subjects and in patients with phaeochromocytoma. Clin Exp Pharmacol Physiol 1992; 19: 287-290.

134) Bright TP, Sandage BW, Jr., Fletcher IIP: Selected cardiac and metabolic responses to pseudoephedrine with exercise. J Clin Pharmacol 1981;21(11-12 Pt 1):488-492.

135) Smith CV, Rayburn WF, Anderson JC, Duckworth AF, Appel LL: Effect of a single dose of oral pseudoephedrine on uterine and fetal Doppler blood flow. Obstet Gynecol 1990; 76(5 Pt 1): 803-806.

136) Rombaut NEI, Alford C, Hindmarch I. Effects of oral administration of different formulations of pseudoephedrine on day- and night-time CNS activity. Med Sci Res 1989;17:831-834.

137) Clemons JM, Crosby SL. Cardiopulmonary and subjective effects of a 60 mg dose of pseudoephedrine on graded treadmill exercise. J Sports Med Phys Fitness 1993;33:405-412.

138) Gillies H, Derman WE, Noakes TD, Smith P, Evans A, Gabriels G. Pseudoephedrine is without effects during prolonged exercise. J Appl Physiol 1996;81:2611-2617.

139) Swain RA, Harsha DM, Baenziger J, Saywell RM Jr. Do pseudoephedrine and phenylpropanolamine improve maximum oxygen uptake and time to exhaustion. Clin J Sports Med 1997;7:168-173.

140) Laitinen LA, Empey DW, Bye C, Britton MG, McDonnell K, Hughes DTD. A comparison of the bronchodilator action of pseudoephedrine and ephedrine in patients with reversible airway obstruction. Eur J Clin Pharmacol 1982;23: 107-109.

141) Adams SS, Bough RG, Cliffe BE, Dickinson W, Lessel B, McCullough KF, Mills RFN, Nicholson JS, Williams GAH: Some aspects of the pharmacology, metabolism and toxicology of ibuprofen. Rheum Phys Med Suppl 1970: 9-14.

142) Anonymous. Acute Overdose Manual. Sudafed. Burroughs Wellcome Co; 1982: 99.

143) Packman EW, Doyle G, Koronkiewicz K, Jayawardina S, Cooper SA: Onset of analgesia of ibuprofen liquigels (400 mg) compared to acetaminophen caplets (1000 mg) in the treatment of tension headache. J Clin Pharmacol 1998; 38: 876.

144) USPDI 2002, p.426-427.

145) Fommei E, Ghione S, Palla L, Ragazzini A, Gazzetti P, Palombo C, Giaconi S: Inhibition of prostaglandins and angiotensin II: Effects on renal function in hypertensive patients. Agents Actions Suppl 1987; 22: 183-189.

146) Cook ME, Wallin JD, Thakur VD, Kadowitz PJ, McNamara DB, Garcia MM, Lipani JJ, Poland M: Comparative effects of nabumetone, sulindac and ibuprofen on renal function. J Rheumatol 1997; 24: 1137-1144.

147) Minuz P, Lechi A, Arosio E, Degan M, Capuzzo MG, Lechi C, Corsato M, Dalla Riva A, Velo GP: antihypertensive activity of enalapril. Effect of ibuprofen and different salt intakes. J Clin Hypertens 1987; 3: 645-653.

148) Jorgenson HS, Christensen HR, Kampmann JP: Interaction between digoxin and indomethacin or ibuprofen. Br J Clin Pharmacol 1991; 31(I): 108-110.

149) Johnson AG, Nguyen TV, Day RO: Do non-steroidal anti-inflammatory drugs affect blood pressure? Ann Intern Med 1994; 121: 289-300.

150) Pope JG, Anderson JJ, Felson DT: A meta-analysis of the effects of non-steroidal anti-inflammatory drugs on blood pressure. Arch Intern Med 1993; 153: 477-484.

151) Davies JG, Rawlins DC, Busson M: Effect of ibuprofen on blood pressure control by propranolol and benzofluazide. J Intern Med Res 1988; 16: 173-181.

152) Houston MC, Weir M, Gray J, Ginserg D, Szeto C, Kathlenen PM, Sugimoto D, Lefkowitz M, Runde M: The effects of non-steroidal anti-inflammatory drugs on blood pressure of patients with hypertension controlled by verapamil. Arch Intern Med 1995; 155: 1049-1054.

153) USP DI. Drug Information for the Health Care Professional, Anti-Inflammatory Drugs, Nonsteroidal (Systemic). Thomson MICROMEDEX, 2005; 1:390.

154) Sudafed Nasal Decongestant Tablets 30 mg: Monographs from the 2002 Physicians Desk Reference. Montvale, New Jes, Doyle R, Culpepper-Morgan JA: Medical Economics Company Inc., 2002.

155) Ashraf E, Ford, L, Geetha R, Cooper S: Safety profile of ibuprofen suspension in young children. Inflammopharmacology 1999, in press.

156) Graves DA, Wecker MT, Meyer MC, Straughn AB, Amsel LP, Hinsvark ON, Bhargana AK, Rotenberg KS. Influence of a standard meal on the absorption of controlled-release pseudoephedrine suspension. Biopharm Drug Dispos 1988;9:267-272.

157) Simons FER, Gu X, Watson WTA, Simons KJ. Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. JPediatr 1996;129:729-734.

158) Autret E, Breart G, Jonvile AP, Courcier S, Lasalle C, Goehrs IM: Comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics. Eur J Clin Pharmacol1994; 46: 197-201.

159) Data on File. A placebo-controlled comparison of the nasal decongestant effect of the combination of ibuprofen 400 mg with pseudoephedrine 60 mg to pseudoephedrine 60mg on nasal airway resistance in patients with acute upper respiratory tract infection. Whitehall-Robins Healthcare Clinical Study WM-389; 1991.

160) Benson MK. Maximal nasal inspiratory flow rate: its use in assessing the effect of pseudoephedrine in vasomotor rhinitis. Eur J Clin Pharmacol 1971;3:182-184.

161) Data on File. A single-dose, double-blind, parallel, randomized, controlled study of nasal airflow rates in patients with nasal congestion treated with ibuprofen 200 mg and pseudoephedrine 30 mg compared with pseudoephedrine 30 mg, 45 mg, or 60 mg.Whitehall-Robins Healthcare Clinical Study WM-315A; 1987.

162) Spielberg SP, Schulman ill: A possible reaction to pseudoephedrine in a patient with phenylketonuria (letter). J Pediatr 1977; 90(6):1026.

163) Product Monograph - **ADVIL COLD & SINUS ADVIL COLD & SINUS DAYTIME** Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP 200 mg/30 mg Caplets **ADVIL COLD & SINUS LIQUI-GELS** Ibuprofen (free acid and potassium salt) and Pseudoephedrine Hydrochloride Capsules 200 mg/ 30 mg **CHILDREN'S ADVIL COLD** Ibuprofen and Pseudoephedrine Hydrochloride Suspension 100 mg/ 15 mg per 5 mL, GlaxoSmithKline Consumer Healthcare Inc. Control No. 238677, Date of Revision: May 14, 2020.

PART III: CONSUMER INFORMATION

COLD & SINUS RELIEF CAPSULES
Ibuprofen and Pseudoephedrine Hydrochloride Capsules

This leaflet is part III of a three-part "Product Monograph" published when COLD & SINUS RELIEF CAPSULES was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about COL D & SINUS RELIEF CAPSULES. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Fast, effective temporary relief of the symptoms of colds including sore throat pain, sinus pain, nasal congestion, headache, fever, body aches and pains.

What it does:
Ibuprofen reduces pain and fever. Pseudoephedrine hydrochloride is a nasal decongestant.

When it should not be used:
Do not use COLD & SINUS RELIEF CAPSULES if you have or are:

- allergic/hypersensitive to acetylsalicylic acid (ASA), ibuprofen, other salicylates, other NSAIDs, pseudoephedrine or other sympathomimetic amines or any of COLD & SINUS RELIEF CAPSULES ingredients (Refer to the nonmedicinal ingredients section of this insert),
- active or recurrent stomach ulcer or gastrointestinal bleeding or active inflammatory bowel disease (e.g. Crohn's, colitis),
- taking a monoamine oxidase inhibitor (MAOI; e.g. drugs for depression or Parkinson's disease) or for 14 days after stopping the MAOI drug, ASA or other NSAIDs including any other ibuprofen product,
- nasal polyps (swelling of the inside of the nose),
- asthma,
- allergic manifestations such as 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 heart disease,
- right before or after heart surgery,
- serious liver disease,
- severe kidney disease,
- thyroid disease,
- Raynaud's Syndrome (a disorder of the circulatory system),
- Systemic Lupus Erythematosus,
- or if you are in your third trimester of pregnancy.

What the medicinal ingredients are:
Ibuprofen and pseudoephedrine hydrochloride.

What the nonmedicinal ingredients are:
D&C Yellow no.10, FD&C Red no.40, gelatin, polyethylene glycol, potassium hydroxide, propylene glycol, and sorbitol sorbitan solution.

The sorbitol sorbitan solution contains sorbitan, sorbitol, mannitol and high polychains.

The capsule shells imprinted with black edible ink contains hypromellose, iron oxide black and propylene glycol.

What dosage forms it comes in:
Each capsule contains ibuprofen 200 mg and pseudoephedrine hydrochloride 30 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- If you have glaucoma or difficulty in urination due to an enlarged prostate, do not take this drug unless directed by a doctor.
- Caution in those with heart failure, high blood pressure or other conditions that may cause excess fluid collecting in tissues.
- Caution in patients at risk of gastrointestinal tract irritation, including those with a history of a 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 acetylsalicylic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs, have 3 or more alcoholic drinks every day while using this product.
- Caution in patients at risk of kidney problems, including the elderly or those using diuretics.
- Use during pregnancy or nursing should be avoided.
- Stop use immediately if you have difficulty or pain when urinating.

BEFORE you use COLD & SINUS RELIEF CAPSULES talk to your doctor or pharmacist if you have:

- blood clotting disorder (such as hemophilia),
- breathing problems or chronic lung disease (such as chronic bronchitis),
- diabetes,
- difficulty in urination due to prostate enlargement,
- glaucoma,
- high blood pressure,
- mild to moderate kidney disease,
- mild to moderate liver disease,

- any other serious disease,
- are 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 or are taking any other drug including over the counter drugs.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking:

- a MAOI or if you have stopped taking one within the past two weeks.
- ASA or other anti-inflammatory or pain medication.

Drugs that may interact with COLD & SINUS RELIEF CAPSULES include:

- Acetaminophen
- acetylsalicylic acid (ASA),
- allergy medications,
- anticoagulants (blood thinning medications),
- antidepressants,
- anti-hypertensives (blood pressure medications),
- antibiotics (levofloxacin),
- benzodiazapines,
- cold medications,
- corticosteroids,
- cyclosporine,
- diabetes medication (including insulin and oral antidiabetic agents),
- digoxin,
- diuretics (water pills),
- lithium,
- methotrexate,
- monoamine Oxidase Inhibitors,
- nonsteroidal anti-inflammatory drugs (NSAIDs); including naproxen and ibuprofen,
- phenytoin
- probenecid
- thyroxine

Tell your doctor or pharmacist what prescription or non-prescription drugs you are taking or plan to take.

Do not smoke or drink alcohol while using this product.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults and children 12 to 65 years: Take 1 or 2 capsules every 4 to 6 hours as needed. Do not exceed 6 capsules in 24 hours, unless directed by a doctor.

Do not give to children under 12 unless directed by doctor. Do not use longer than 3 days for a fever or 5 days for pain or cold symptoms.

Overdose:

If you think you have taken too much COLD & SINUS RELIEF CAPSULES, contact your healthcare professional, hospital emergency department or regional poison control center immediately, even if there are no symptoms.

Missed Dose:
Continue to take 1 or 2 capsules every 4 to 6 hours as needed after a missed dose. Do not take twice the recommended dose following a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.
COLD & SINUS RELIEF CAPSULES may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness.

Stop use and contact a doctor or pharmacist if these symptoms worsen or persist.

The risk of having side effects may be decreased by using the smallest dose for the shortest duration of time.

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

Symptom / effect		Talk with your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon	Symptoms of allergic reaction, including: rash, severe itching/ redness, blisters, swelling, or trouble breathing			T
	Blood in vomit, bloody or black stools			T
	Abdominal pain, vomiting, diarrhea		T	
	Ringing or buzzing in the ears / dizziness		T	
	Change in vision,		T	
	Fluid retention		T	

This is not a complete list of side effects. For any unexpected effects while taking COLD & SINUS RELIEF CAPSULES, 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

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

HOW TO STORE IT

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

Keep out of reach of children. This package contains enough medicine to seriously harm a child.

MORE INFORMATION

If you want more information about COLD & SINUS RELIEF CAPSULES:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

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

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