PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

COLD + SINUS

Ibuprofen and Pseudoephedrine Hydrochloride Tablets

Caplets, 200 mg/30 mg, for oral use

USP

ATC Code: M01AE51 Ibuprofen, Combinations

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS 3 SERIOUS WARNINGS AND PRECAUTIONS BOX 7 WARNINGS AND PRECAUTIONS; Monitoring and Laboratory Tests – Pregnancy; Special Populations	08/2025

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

COLD + SINUS (Ibuprofen and Pseudoephedrine Hydrochloride Tablets) is 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.

1.1 Pediatrics

Pediatrics (<12 years of age): No data for COLD + SINUS is available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 COLD + SINUS in this population is not recommended (See 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

2 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. The potential for cross-reactivity between different NSAIDs must be kept in mind.
- COLD + SINUS 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 9 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 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 (See 9 DRUG INTERACTIONS).
- Ibuprofen should not be used during the third trimester of pregnancy because the risk of premature closure of the ductus arteriosus, and prolonged parturition.
- 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 7 WARNINGS AND PRECAUSTIONS, Fluid and Electrolyte Balance)
- Immediately before or following heart surgery.
- In patients with thyroid disease.
- In patients with Raynaud's Syndrome.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 (See 7 WARNINGS AND PRECAUTIONS, General).
- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See 7 WARNINGS AND PRECAUTIONS, 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Fluid and Electrolyte Balance and 9 DRUG INTERACTIONS, Antihypertensives).
- Use with 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 7 WARNINGS AND PRECAUTIONS, Gastrointestinal and 9 DRUG INTERACTIONS, Anticoagulants).
- Use with 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 7 WARNINGS AND PRECAUTIONS, Renal).
- If persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria and cystitis occur, the drug should be stopped immediately (See 7 WARNINGS AND PRECAUTIONS, Genitourinary).
- Ibuprofen is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see 2 CONTRAINDICATIONS).
- Caution should be exercised in prescribing ibuprofen products during the first and second trimesters of pregnancy or breastfeeding. Use of NSAIDS at approximately 20 weeks of gestation or later may cause oligohydramnios, and renal dysfunction including renal failure (See 7 WARNINGS AND PRECAUTIONS, Oligohydramnios/Neonatal Renal Impairment, Pregnant Women and Breastfeeding).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Do not take for fever for more than 3 days or for more than 5 days for cold symptoms/pain.
- Do not take for sore throat pain for more than 2 days.
- Patients older than 65 years should not use COLD + SINUS.
- The lowest effective dose should be used for the shortest possible duration.

4.2 Recommended Dose and Dosage Adjustment

- Adults under 65 years of age and children over 12 years of age: Take 1 or 2 caplets every 4 to 6 hours as needed. No more than 6 caplets are to be taken in 24 hours, unless directed by a physician.

4.4 Administration

See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment.

4.5 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.

5 OVERDOSAGE

Symptoms of Overdosage

COLD + SINUS contains 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. 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.

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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

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. 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. 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. A 6-year-old child became comatose after ingesting 6 g of ibuprofen. 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.

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. 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.

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. 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. 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).

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). 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. 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.

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 acetylcysteine solution (Mucomyst) and charcoal and was discharged from the hospital after a 2-day stay.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Caplet: 200 mg Ibuprofen and 30 mg Pseudoephedrine Hydrochloride	Colloidal silicon dioxide, croscarmellose sodium, iron oxide red, iron oxide yellow, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, pregelatinized starch, sodium lauryl sulphate, stearic acid, talc, titanium dioxide, xanthan gum.

Description

COLD + SINUS caplets are brown coloured, oval, biconvex film-coated caplets having '271' debossing on one side and plain on the other side. They are available in bottles of 40, 50, 72 and 102 caplets and blister packs of 10 and 20 caplets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.

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

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

In case of an overdose, medical help or a poison control centre should be contacted immediately. Prompt medical attention is critical, even in the absence of signs or symptoms.

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.

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

COLD + SINUS 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. The PVCs disappeared within a few days after discontinuation of the medication.

There have been reports of acute systemic vasoconstrictive events with pseudoephedrine.

Significant examples include:

- Acute Coronary Syndrome (ACS): Symptoms include sudden chest pain, tightness, heavy sweating and dyspnoea at rest.
- Posterior reversible encephalopathy syndrome (PRES)/reversible cerebral vasoconstriction syndrome (RCVS): Symptoms included sudden onset of severe headache, nausea, vomiting, and visual disturbances. Most cases improved or resolved within a few days following appropriate treatment.

Pseudoephedrine should be discontinued immediately and medical advice sought if any signs/symptoms of vasoconstrictive events develop.

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). A 37-year-old woman admitted to taking 100 to 150 30-mg pseudoephedrine tablets daily. 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 2 CONTRAINDICATIONS.

Endocrine and Metabolism

Patients with thyroid disease should not take this drug. See 2 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 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 2 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 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases. The incidence of these complications increases with increasing dose.

COLD + SINUS 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 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 COLD + SINUS 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. 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. Pseudoephedrine should be discontinued immediately and medical advice sought if any signs/symptoms of ischemic colitis develop.

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 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. Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur. (See 9 DRUG INTERACTIONS).

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

Hepatic/Biliary/Pancreatic

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver function tests (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. 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 2 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.

Monitoring and Laboratory Tests - Pregnancy

If ibuprofen products are administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women be closely monitored for amniotic fluid volume since these products may result in reduction of amniotic fluid volume and even oligohydramnios (see 7 WARNINGS AND PRECAUTIONS, Special Populations). Ibuprofen products are contraindicated for use in the third trimester of pregnancy.

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 non-steroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Patients with glaucoma should be closely monitored.

Peri-Operative Considerations

See 2 CONTRAINDICATIONS. In general, NSAIDs are discontinued prior to surgeries to decrease the risk of post-operative bleeding.

Psychiatric

See 7 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 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. 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.

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 2 CONTRAINDICATIONS).

Sensitivity/Resistance

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

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.

7.1 Special Populations

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including ibuprofen products, at approximately 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some more severe cases, neonatal respiratory, musculoskeletal and renal problems (see 16 NON-CLINICAL TOXICOLOGY).

Published studies and post-marketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment, or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary anywhere from the middle (onset approximately 20 weeks) to the end of the second trimester of pregnancy, it is recommended that the use be limited to the lowest effective dose and shortest duration possible.

Consider ultrasound monitoring of fetal well-being, including of amniotic fluid volume assessment if treatment with ibuprofen products extends beyond 48 hours. It is recommended that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inform pregnant women not to use ibuprofen products and other NSAIDs from the third trimester of pregnancy because of the risk of the premature closing of the fetal ductus arteriosus (see 2 CONTRAINDICATIONS). If treatment with ibuprofen products is needed for a pregnant woman anywhere from the middle (onset approximately 20 weeks gestation) to the end of the second trimester of pregnancy, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours.

7.1.1 Pregnant Women

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

COLD + SINUS is contraindicated for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus.

Because of the known effects of NSAIDs on the fetal cardiovascular system, use of ibuprofen during late pregnancy should be avoided. (see 7 WARNINGS AND PRECAUTIONS, Oligohydramnios/Neonatal Renal Impairment).

Caution should be exercised in prescribing ibuprofen products to women who are trying to conceive, or during the first and second trimesters of pregnancy (See 16 NON-TOXICOLOGY).

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various

malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. However, animal reproduction studies are not always predictive of human response. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats.

7.1.2 Breast-feeding

Use of COLD + SINUS product should be avoided during nursing.

7.1.3 Pediatrics

Pediatrics (<12 years of age): No data for COLD + SINUS products are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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 products are not indicated for use in patients over 65 years of age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Serious adverse reactions occur uncommonly with COLD + SINUS. The most common reactions include heartburn, constipation, nausea, bloating, nervousness or sleeplessness.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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.

In a placebo-controlled, double-blind clinical study of 58 subjects with rhinovirus infection, pseudoephedrine given alone or with ibuprofen was well-tolerated. 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.

8.5 Post-Market Adverse Reactions

Safety Studies of Ibuprofen - adults

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. 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, a meta-analysis, and a literature review, 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. 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. 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, 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 simultaneous use of hepatotoxic medication and the presence of rheumatoid arthritis.

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 3-6 months and in about 2-4% of patients treated for 1 year. The risk continues beyond 1 year. The incidence of GI complications increases with increasing dose.

Incidence 3-9%: nausea, epigastric pain, heartburn. Incidence 1-3%: 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 2 CONTRAINDICATIONS). Causal relationship unknown: fever, serum sickness, lupus erythematosus.

Central Nervous System

Incidence 3-9%: dizziness. Incidence 1-3%: 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 3-9%: rash (including maculopapular type). Incidence 1-3%: 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 1-3%: tinnitus. Incidence <1%: amblyopia (blurred and/or diminished vision, scotomata, and/or changes in colour vision). Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination. Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

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 1-3%: decreased appetite, oedema, fluid retention.

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, 411 reports were received 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 (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	Musculoskeletal	Musculoskeletal

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
	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. 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 42.2°C. 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. 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.

Pseudoephedrine was reported to cause coronary artery spasm and myocardial infarction in a 28-year-old man. 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. 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. 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.

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. 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. 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. 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.

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. 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.

9 DRUG INTERACTIONS

9.1 Serious 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 2 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 selective serotonin reuptake inhibitors (SSRIs) may increase the risk of GI adverse events (e.g., ulceration and bleeding).
- With glucocorticoids may increase the risk of GI adverse events (e.g., ulceration and bleeding).
- 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 2 CONTRAINDICATIONS).

9.2 Drug Interactions Overview

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

9.3 Drug-Behavioural Interactions

Avoid drinking alcohol while taking Ibuprofen products, as this may increase the risk of serious stomach bleeding. Avoid smoking while taking COLD + SINUS or other NSAIDs.

9.4 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 COLD + SINUS is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs
The use of COLD + SINUS 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 2 CONTRAINDICATIONS).

Antacids
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
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 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 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 showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β-adrenergic blockers. Houston et al 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. 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 hydrochlorothiazide and fosinopril who received ibuprofen 2400 mg/day for one month. In contrast, Minuz 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
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.

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

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
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
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 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 (See 2 CONTRAINDICATIONS).

Selective Serotonin Reuptake Inhibitors (SSRIs)
Studies report an increased risk of gastrointestinal (GI) ulceration and bleeding when Ibuprofen as well as other NSAIDs are taken concomitantly with selective serotonin reuptake inhibitors (SSRIs) than when either class of drugs is taken alone (See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

Other Drugs
COLD + SINUS 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 in conjunction with probenecid, thyroxine, cyclosporine, antibiotics (e.g. levofloxacin), phenytoin, corticosteroids or benzodiazepines.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbs have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ibuprofen

Like other nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen is an analgesic, antipyretic, and anti-inflammatory medication. The principal mechanism of action of ibuprofen and other NSAIDs is inhibition of prostaglandin biosynthesis. 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. 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, percent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache.

Pseudoephedrine Hydrochloride

Pseudoephedrine acts directly on both alpha- and, to a lesser degree, beta-adrenergic receptors. 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.

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. Drainage of sinus secretions is increased, and obstructed eustachian ostia may be opened.

10.2 Pharmacodynamics

Ibuprofen

Animal Pharmacology

Cyclooxygenase inhibitors such as ibuprofen and other NSAIDs reduce thromboxane A2 production and release, thereby decreasing platelet aggregation. Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated in vivo by prevention of platelet disposition in aortopulmonary arterial bypass grafts in dogs. The drug's protective action against pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to inhibition of platelet aggregation. The decreased platelet aggregation may be due in part to a reduction in membrane fluidity.

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 C14-labeled ibuprofen. 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.

Human Pharmacology

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. The bronchodilating potencies of pseudoephedrine and ephedrine in anaesthetized dogs are approximately equal, but pseudoephedrine produces a greater degree of nasal decongestion with less cardiovascular involvement than ephedrine. Pseudoephedrine increases plasma corticosterone levels and produces hyperglycemia in mice.

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. 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. 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.

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. 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. 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. In other studies, pseudoephedrine at standard doses had no significant effect on systolic or diastolic blood pressure. In subjects with phaeochromocytoma, pseudoephedrine increased blood pressure and plasma noradrenaline concentration.

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. 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. 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. 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. In a study of the effects of pseudoephedrine on day- and nighttime 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). Improvements were seen in psychomotor function (choice reaction time) and information processing (critical flicker fusion). Detrimental effects on nighttime 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.

Pseudoephedrine administered as a single 60-mg dose or 120-mg dose or administered at 1–2 mg/kg 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.

The effect of pseudoephedrine as a bronchodilator is small at a 210-mg dose and is approximately one-

half that of ephedrine. In a study of subjects with reversible airway obstruction, pseudoephedrine at 60 mg and 180 mg produced no significant bronchodilation.

10.3 Pharmacokinetics

Absorption

Ibuprofen

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

Pseudoephedrine Hydrochloride

After oral administration, pseudoephedrine is readily and completely absorbed from the gastrointestinal tract, with no evidence of first-pass metabolism. 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.

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. Food appeared to delay absorption of pseudoephedrine from syrup formulations and controlled-release capsules but had no effect on absorption from a suspension.

Distribution:

Ibuprofen

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

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. Pseudoephedrine concentration-time data after oral administration are well described using a one body compartment model with first-order absorption and elimination. The approximate plasma clearance of pseudoephedrine is 0.44 L/h/kg.

Metabolism:

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. S-(+) ibuprofen is the pharmacologically active enantiomer.

The plasma half-life (t½) of ibuprofen in adults and children is 1.5 - 2.0 hours. There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl] propionic acid and 2-[4-(2-hydroxy-2-methyl)propyl]propionic acid, have been identified in plasma and in urine. 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.

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

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. 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.

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. 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. 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. Over the 30-mg to 60-mg dose range, the kinetics of pseudoephedrine in children were not dose dependent.

Elimination

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. 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. 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. Norpseudoephedrine recovery from urine ranged from less than 1% to 6.2%.

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

pseudoephedrine.

11 STORAGE, STABILITY AND DISPOSAL

COLD + SINUS should be stored in tightly closed containers at room temperature (15-30˚C).

Keep out of reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ibuprofen

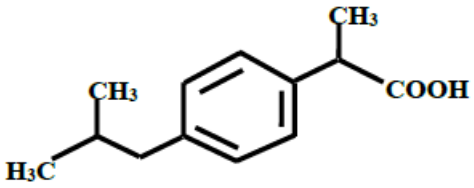
Chemical name: α-methyl-4-(2-methylpropyl) benzeneacetic acid

Other names: p-isobutylhydratropic acid

2-(4-isobutylphenyl)-propionic acid

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

Structural formula:



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

Product Characteristics:

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: 75-77 °C

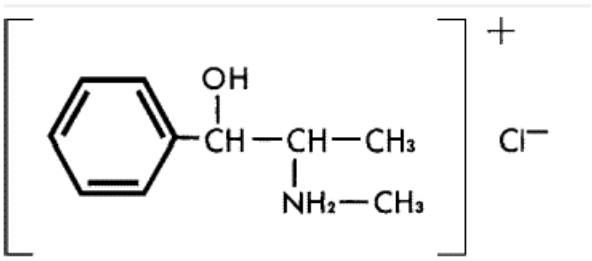
Proper name: Pseudoephedrine hydrochloride

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

Other names: (+)-Pseudoephedrine hydrochloride

Molecular Formula and molecular mass: $C_{10}H_{15}NO \cdot HCl$, 201.70 daltons

Structural Formula:



Physicochemical Properties: 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: 180-186 °C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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, headache, and muscle aches in adults. The antipyretic efficacy of ibuprofen has been demonstrated in adults at doses of 200 and 400 mg and in children at doses of 5 to 10 mg/kg. Ibuprofen is effective in treating the pain of sore throat in children.

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. Time-weighted sums of changes in nasal airflow relative to baseline were greater with both active treatments than with placebo (Table 3).

Table 3 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

Treatment	N	Mean Nasal Air Flow Rate (mL/sec)		P Value versus Placebo[a]	
		First 4 Hours Post dose	Entire 6-Hour Period Postdose	First 4 Hours Postdose	Entire 6-Hour 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 post dose).

Pseudoephedrine at a dose of 60 mg increases maximal nasal inspiratory flow rate and produces objective improvement in nasal airway resistance. A single 60-mg oral dose of pseudoephedrine produced marked nasal decongestant effects within 30 minutes of administration, lasting for at least 4 hours. 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. 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. There was no significant change in nasal area as measured by active posterior rhinomanometry.

In a double-blind, randomized study, 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 4).

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

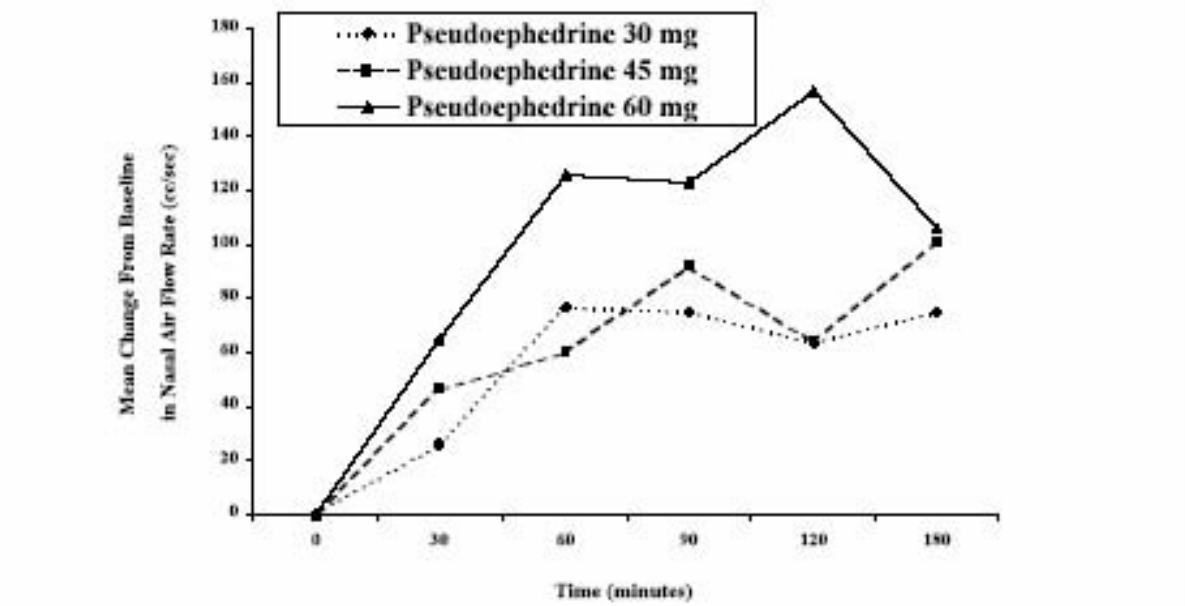


Table 4 Mean Nasal Air Flow (Standard Deviation) after Single Doses of Pseudoephedrine (30, 45, or 60 mg) or Ibuprofen 200 mg plus Pseudoephedrine 30 mg in Subjects with Allergic Rhinitis

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 (143)	328 (119)	393 (157)	454 (217)	451 (196)	485 (214)	435 (136)
Ibuprofen 200 mg + pseudoephedrine	28	416 (147)	365 (143)	416 (196)	454 (173)	429 (154)	468 (177)	477 (201)
30 mg								

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

14.3 Comparative Bioavailability Studies

A randomized, open label, single dose, two-way crossover, bioequivalence study was conducted with 24 healthy adult Asian human male subjects under fasting conditions comparing COLD + SINUS (200 mg ibuprofen/30 mg pseudoephedrine hydrochloride) (Vita Health Products Inc.) to Advil Cold and Sinus Caplets (200 mg ibuprofen/30 mg pseudoephedrine hydrochloride) (Wyeth Consumer Healthcare Inc.).

Ibuprofen (1 x 200 mg/30 mg ibuprofen/pseudoephedrine hydrochloride caplet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test**[1]	**Reference**[2]	**% Ratio of Geometric Means**	**90 % Confidence Interval**
AUC_T (µg.h/mL)	46.14 48.88 (34.77)	46.45 48.74 (30.05)	99.33	93.86 – 105.11
AUC_I (µg.h/mL)	48.46 51.13 (33.92)	48.95 51.02 (28.70)	98.98	93.64 – 104.62
C_{MAX} (µg/mL)	15.07 15.62 (28.52)	14.58 15.01 (22.84)	103.35	93.22 – 114.59
T_{MAX}[3] (h)	2.05 (48.34)	2.13 (44.70)	Not applicable	Not applicable
$T_{½}$[4] (h)	1.89 (20.06)	1.91 (20.31)	Not applicable	Not applicable

[1] Cold + Sinus (200 mg ibuprofen/30 mg pseudoephedrine HCl caplets) Vita Health Products Inc., Canada.

[2] Advil Cold & Sinus (200 mg ibuprofen/30 mg pseudoephedrine HCl caplets) GlaxoSmithKline Consumer Healthcare ULC were purchased in Canada.

[3] Expressed as either the arithmetic mean (CV%) or the median (range) only.

[4] Expressed as the arithmetic mean (CV%) only.

Pseudoephedrine (1 x 200 mg/30 mg ibuprofen/pseudoephedrine hydrochloride caplet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test**[5]	**Reference**[6]	**% Ratio of Geometric Means**	**90 % Confidence Interval**
AUC_T (µg.h/mL)	12.55 12.84 (22.40)	13.65 14.05 (25.88)	91.98	87.89 – 96.26
AUC_I (µg.h/mL)	12.97 13.26 (21.96)	14.25 14.72 (27.97)	91.04	86.67 – 95.64
C_{MAX} (µg/mL)	1.72 1.78 (27.14)	1.68 1.74 (27.27)	102.53	96.47 – 108.96
T_{MAX}[7] (h)	1.68 (39.68)	1.94 (44.25)	Not applicable	Not applicable
$T_{½}$[8] (h)	4.21 (14.82)	4.58 (23.52)	Not applicable	Not applicable

[5] Cold + Sinus (200 mg ibuprofen/30 mg pseudoephedrine HCl caplets) Vita Health Products Inc., Canada.

[6] Advil Cold & Sinus (200 mg ibuprofen/30 mg pseudoephedrine HCl caplets) GlaxoSmithKline Consumer Healthcare ULC were purchased in Canada.

[7] Expressed as either the arithmetic mean (CV%) or the median (range) only.

[8] Expressed as the arithmetic mean (CV%) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Ibuprofen

Single Dose Toxicity Studies

Single-dose toxicity studies have been conducted in mice, rats, and dogs.

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
	Intraperitoneal	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.

Multi Dose Studies

The primary toxic effect of ibuprofen in repeated doses in rats is intestinal damage. 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.

Carcinogenicity

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. 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).

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.

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.

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.

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. 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.

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
Dobs, mongrel	Oral	307

17 SUPPORTING PRODUCT MONOGRAPHS

ADVIL COLD AND SINUS Advil Cold and Sinus (caplets, 200 mg ibuprofen/30 mg pseudoephedrine HCl), submission control number 282832, Product Monograph, GlaxoSmithKline Consumer Healthcare ULC. (APR 23, 2025).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

COLD + SINUS

Ibuprofen and Pseudoephedrine Hydrochloride Tablets USP

Read this carefully before you start taking **COLD + SINUS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **COLD + SINUS**.

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.
- Use with caution in those with heart failure, high blood pressure or other conditions that may cause excess fluid collecting in tissues.
- Use with caution in patients at risk of gastrointestinal tract irritation, including those with a history of peptic ulcer. Symptoms may include feeling faint, vomiting blood, bloody or black stools. 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, or have 3 or more alcoholic drinks every day while using this product.
- Use with caution in patients at risk of kidney problems, such as those with heart failure, liver disease, the elderly or those using diuretics.
- COLD + SINUS should not be used during the third trimester of pregnancy.
- Use during the first and second trimesters of pregnancy or nursing should be avoided unless directed by your health care professional.
- Stop use immediately if you observe blood in the urine or you develop urgent, frequent, painful or difficult urination.

What is COLD + SINUS used for?

- Fast, temporary relief of the symptoms of colds including sore throat pain, sinus pain, nasal congestion, headache, fever, body aches and pains.

How does COLD + SINUS work?

Ibuprofen reduces pain and fever. Pseudoephedrine hydrochloride is a nasal decongestant.

What are the ingredients in COLD + SINUS?

Medicinal ingredients: Ibuprofen and pseudoephedrine hydrochloride.

Non-medicinal ingredients: Colloidal silicon dioxide, croscarmellose sodium, iron oxide red, iron oxide yellow, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, pregelatinized starch, sodium lauryl sulphate, stearic acid, talc, titanium dioxide, xanthan gum.

COLD + SINUS comes in the following dosage forms:

Each caplet contains ibuprofen 200 mg and pseudoephedrine hydrochloride 30 mg.

Do not use COLD + SINUS if you have or are:

- allergic/hypersensitive to acetylsalicylic acid (ASA), ibuprofen, other salicylates, other NSAIDs, pseudoephedrine or other sympathomimetic amines or any of the ingredients in COLD + SINUS (Refer to the nonmedicinal ingredients section of this insert)
- active or recurrent stomach ulcer or gastrointestinal (GI) 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
- in your third trimester of pregnancy

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take COLD + SINUS. Talk about any health conditions or problems you may have, including if you have or are:

- 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
- under doctor's care for any serious condition,
- trying to conceive, in your first or second trimester of pregnancy or if you are breastfeeding
- in the second trimester of pregnancy, your use of NSAIDs, like ibuprofen products, may need to be monitored by a health care practitioner due to the rare risk of kidney problems in the unborn baby which may result in decreased amniotic fluid volume and other complications
- taking medication for weight control

- taking any other drug including over the counter drugs

Other warnings you should know about:

Do not smoke or drink alcohol while using this product.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with COLD + SINUS:

- acetaminophen
- acetylsalicylic acid (ASA)
- allergy medications
- anticoagulants (blood thinning medications)
- selective serotonin reuptake inhibitors (SSRIs) used to treat depression
- anti-hypertensives (blood pressure medications)
- antibiotics (levofloxacin)
- benzodiazepines
- 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

How to take COLD + SINUS:

Usual dose:

- Adults and children over 12 to 65 years: Take 1 or 2 caplets every 4- 6 hours as needed. Do not exceed 6 caplets in 24 hours, unless directed by a doctor.
- Do not give to children under 12.

Overdose:

If you think you, or a person you are caring for, have taken too much COLD + SINUS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Continue to take 1 or 2 caplets every 4-6 hours as needed after a missed dose. Do not take twice the

recommended dose following a missed dose.

What are possible side effects from using COLD + SINUS?

Stop use and ask a doctor if:

- you show signs of stomach bleeding
- sore throat pain lasts more than 2 days
- symptoms worsen or last more than 5 days
- fever lasts more than 3 days
- you are nervous, dizzy or can't sleep
- any new symptoms appear

These are not all the possible side effects you may have when taking COLD + SINUS. If you experience any side effects not listed here, tell your healthcare professional.

Take with food or milk if upset stomach occurs.

COLD + SINUS may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness. Stop use and contact a healthcare professional 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 and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Sudden severe headache accompanied by confusion, seizures, vomiting sensation or changes in vision. These may be signs of a serious condition.			✓
Symptoms of allergic reaction, including rash, severe itching / redness, blisters, swelling, or trouble breathing			✓
Blood in vomit, bloody or black stools			✓
Abdominal pain, vomiting, diarrhea		✓	
Ringing or buzzing in the ears / dizziness		✓	
Change in vision		✓	
Fluid retention		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.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.

Storage:

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

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

If you want more information about COLD + SINUS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.vitahealth.ca, or by calling 1-877-637-7557.

This leaflet was prepared by Vita Health Products Inc.

Last Revised August 28, 2025