PRODUCT MONOGRAPH

ADVIL® COLD & SINUS PE

200 mg Ibuprofen, 5 mg Phenylephrine Hydrochloride

Caplets

Analgesic/Antipyretic/Decongestant

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Date of Preparation: July 6, 2020

Submission Control No: 239839

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Ibuprofen and Phenylephrine Hydrochloride Caplets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Caplets: ibuprofen 200 mg, phenylephrine hydrochloride 5 mg	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Advil® Cold & Sinus PE is indicated for:

The temporary effective relief of symptoms associated with the common cold including nasal congestion, headache, fever, sinus pain and minor body aches and pains.

Advil® Cold & Sinus PE is a non-prescription analgesic/antipyretic and nasal decongestant preparation.

Geriatrics (> 65 years of age):
Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Therefore the use of Advil Cold & Sinus PE in this population is not recommended **(**see **Warnings and Precautions)**.

Pediatrics (12 years of age and younger):
Safety and efficacy of Advil® Cold & Sinus PE has not been established in the paediatric population. Advil® Cold & Sinus PE is not recommended for children 12 years of age and younger.

CONTRAINDICATIONS

- Active peptic ulcer, a history of recurrent ulceration, concurrent or previous history of gastrointestinal ulcer or bleeding, or active inflammatory disease of the gastrointestinal system, such as ulcerative colitis and Crohns disease.

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

- 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 non steroidal 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.

- Severe 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 (See **Warnings and Precautions -*Renal***).

- Ibuprofen is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects (See **Drug Interactions**).

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

- Pregnant or nursing mothers.

- Advil® Cold & Sinus PE should not be used by patients who have known or suspected hypersensitivity to phenylephrine hydrochloride or other sympathomimetic amines.

- Patients that have been diagnosed with severe high blood pressure or heart disease.

- Immediately before or following heart surgery.

- Patients with Raynaud's Syndrome.

- Patients with systemic lupus erythematosus, as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.

- Use with a prescription monoamine oxidase inhibitor (MAOI) drug or within 14 days of stopping the MAOI drug (See **Drug Interactions**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- $ Patients with glaucoma or difficulty in urination due to enlargement of the prostate gland should not take this drug unless directed by a physician (See *WARNINGS AND PRECAUTIONS, General*).
- $ Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See *WARNINGS AND PRECAUTIONS, Cardiovascular and Fluid and Electrolyte Balance; and DRUG INTERACTIONS, Antihypertensives*).
- $ Caution in patients who might be prone to gastrointestinal tract irritation, particularly those with a history of diverticulosis, or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease (See *WARNINGS AND PRECAUTIONS, Gastrointestinal and DRUG INTERACTIONS, Coumarin-type anticoagulants*).
- $ Caution in patients at greatest risk of renal toxicity, such as those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly (*See WARNINGS AND PRECAUTIONS, Renal*).
- $ If persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria and cystitis occur, the drug should be stopped immediately (See *WARNINGS AND PRECAUTIONS, Genitourinary*).>

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

If nervousness, dizziness, or sleeplessness occurs, use of Advil® Cold & Sinus PE should be discontinued and a physician should be consulted. Advil® Cold & Sinus PE should not be used for more than 3 days for fever of 5 days for pain/cold symptoms. Consult a physician if fever worsens or persists for more than 3 days.

Side effects may be minimized by using the smallest dose (2 caplets) for the shortest duration of time.

Carcinogenesis and Mutagenesis
See **Toxicology – *Carcinogenic Potential***.

Cardiovascular
Use of ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) can cause congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations. Patients with heart disease and high blood pressure should not take this drug unless directed by a physician.

Ear/nose/Throat
See **Contraindications**.

Endocrine and Metabolism
Patients with diabetes or thyroid disease should not take this drug unless directed by a physician. See **Contraindications**.

Fluid and Electrolyte Balance
Fluid retention and oedema have been observed in patients treated with ibuprofen. Therefore, as with many other non steroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Advil Cold & Sinus PE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With non steroidal anti-inflammatory treatment there is 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 (GI)
See **Contraindications**. Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, including ibuprofen.

Minor upper GI problems, such as dyspepsia, are common and usually develop early in therapy. Health care providers should remain alert for ulceration and bleeding in patients treated with Advil® Cold & Sinus PE 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.

Advil® Cold & Sinus PE 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, Advil® Cold & Sinus PE 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. In these cases the physician must weigh the benefits of treatment against the possible hazards. 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 Advil® Cold & Sinus PE therapy when and if these adverse reactions appear.

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, and urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with Advil® Cold & Sinus PE must be stopped immediately to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out [1]. Patients experiencing difficulty urinating due to an enlargement of the prostate gland should not take this drug unless directed by a physician.

Hematologic

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

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

Hepatic / Biliary / Pancreatic

As with other NSAIDs, 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 NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g. eosinophilia, associated with rash, etc.), this drug should be discontinued [1].

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 [1].

The frequency of acute liver injury among 625,307 people who received NSAIDs in England and Wales between 1987 and 1991, was examined [2]. There were 311,716 patients who were prescribed ibuprofen. The incidence of acute liver injury among ibuprofen users was 1.6/100,000; this was the lowest incidence among the 8 NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbrufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were the simultaneous use of hepatotoxic medication or the presence of rheumatoid arthritis. Based on these data, the short-term use of ibuprofen as an analgesic/antipyretic should not be of concern regarding the development of liver disease.

Immune

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

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

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as Advil®. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness [1].

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop, Advil® Cold & Sinus PE should be discontinued and an ophthalmologic examination performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving Advil® Cold & Sinus PE for an extended period of time [1]. Patients with glaucoma should not take this drug unless directed by a physician.

Peri-Operative Considerations

See **Contraindications**. In general, NSAIDs should be discontinued prior to surgeries to decrease the risk of post-operative bleeding [3].

Psychiatric
See **Warnings and Precautions – *Neurologic***.

Renal
Long term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome [1].

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 Advil® Cold & Sinus PE should be considered and patients carefully monitored.

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

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

Sensitivity/Resistance
Patients sensitive to any one of the NSAIDs may be sensitive to any of the other NSAIDs also.

Sexual Function / Reproduction
Not applicable.

Skin
In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they

experience a skin rash, reddening or blisters they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue [1].

Phenylephrine is a rare but well-documented cause of sensitization. Rapid onset, maximal intensity between 12 to 24 hours, and positive patch test results are consistent with Type IV hypersensitivity mechanisms [4, 5]. A single case of occupational contact allergy to phenylephrine is available [6].

Special Populations

Pregnant Women
Advil® Cold & Sinus PE is contraindicated for use during pregnancy.

Nursing Women
Advil® Cold & Sinus PE is contraindicated for use by nursing women.

Pediatrics (12 years of age and younger)
See **Contraindications**.

Geriatrics (>65 years of age)
Use with caution in the elderly is recommended. Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. Most reports of fatal gastrointestinal (GI) events are in this population. Older patients are also less tolerant to and at higher risk of lower esophageal ulceration and bleeding. Advil® Cold & Sinus PE is contraindicated for use in adults over 65 years of age.

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

See "Gastrointestinal Warnings and Precautions" for further advice**.**

Monitoring and Laboratory Tests
For **Warnings and Precautions** related to the use of Advil® Cold & Sinus PE and Monitoring and Laboratory Tests, see *Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal and Subpopulations sections*.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequently reported ADRs associated with NSAID use involve the GI tract (e.g., dyspepsia, heartburn, nausea, abdominal pain); serious ADRs such as peptic ulcer and GI bleeding can occur. CNS effects are also noted frequently (e.g., headache, dizziness, nervousness); occasionally, renal (*e.g.,* renal failure) and dermatologic (*e.g.,* rash) effects are

reported. The incidence and severity of adverse events are dose and duration of use dependent. With use at low doses and for short periods of time (OTC use), the frequency and severity of ADRs are much less frequent and less severe than seen with typical prescription use.

Sympathomimetic drugs are associated with ADRs such as fear, anxiety, tenseness, tremor, hallucinations, seizures, pallor, respiratory difficulty, dysuria, and cardiovascular collapse. In therapeutic doses, phenylephrine (PE) causes little if any central nervous system stimulation, but may cause nervousness, restlessness, anxiety, dizziness, and tremor in some patients. As with other sympathomimetic drugs, PE should be used with caution in hypertensive subjects, hypothyroidism, diabetes mellitus, ischemic heart disease, or prostatic hypertrophy.

For further information please see **Warnings and Precautions**.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A comparative bioequivalence study conducted on Advil® Cold & Sinus PE caplets (200 mg Ibuprofen and 5 mg phenylephrine HCl) versus Motrin® IB 200 mg Tablets and Sudafed PE® Extra Strength 10 mg tablets in 24 Normal, healthy, non-smoking volunteers reported no serious adverse effects [7].

No Adverse Drug Reactions (ADRs) were reported more than once after treatment with Advil® Cold & Sinus PE caplets, Motrin® IB Tablets or Sudafed PE® Extra Strength Tablets. At the end-of-study exam, the most frequent ADR was the following: blood creatinine increased (2/9).

Six subjects experienced a total of 11 ADRs. Three ADRs were "probably" related to the study drug. One subject experienced a total of 2 AEs after administration of Advil® Cold & Sinus PE caplets (200 mg ibuprofen and 5 mg phenylephrine HCl). These consisted of 1 instance each of clammy skin and pallor. The ADRs were both mild in severity and resolved with no action taken.

No ADRs were reported after administration of Motrin® IB 200 mg Tablets or after administration of Sudafed PE® Extra Strength 10 mg Tablets.

Five subjects experienced a total of 9 ADRs during the end-of-study examination. These consisted of 2 instances of blood creatinine increased, and 1 instance each of alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood urea increased, lactate dehydrogenase increased, neutrophil count decreased, total bilirubin increased, and white blood cell count decreased. The ADRs were all mild in severity. Three ADRs resolved with no action taken. Both instances of blood creatinine increased and 1 instance each

of ALT increased, AST increased, blood urea increased, and lactate dehydrogenase increased were not considered to be resolved, as the subjects were lost to follow-up.

Abnormal Hematologic and Clinical Chemistry Findings
No information available.

Post-Market Adverse Drug Reactions

Ibuprofen

Adverse Events with Doses of Ibuprofen ≥ 1200 mg/day:
The following adverse reactions have been noted in patients treated with prescription doses (≥1200 mg/day).

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

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

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 to 9%: nausea, epigastric pain, heartburn.

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

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

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

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

Central Nervous System
Incidence 3 to 9%: dizziness.

Incidence 1 to 3%: headache, nervousness.

Incidence less than 1%: depression, insomnia.

Causal relationship unknown: paresthesias, hallucinations, dream abnormalities.

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

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

Incidence 1 to 3%: pruritus.

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

Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

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

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

Special Senses
Incidence 1 to 3%: tinnitus.

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

Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

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

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

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

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

Hepatic
Incidence less than 1%: hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin, and alkaline phosphatase). Liver enzyme elevations may occur in up to 15% of patients treated with ibuprofen.

Endocrine
Causal relationship unknown: gynecomastia, hypoglycaemic reaction.

Menstrual delays of up to two weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg three times daily, for three days before menses.

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

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

Non-Prescription Experience: Literature (Doses of Ibuprofen ≤1200 mg/day)
One researcher conducted an extensive analysis of published data concerning the relative safety of non-prescription doses of ibuprofen and acetaminophen [8]. Of a total of 96 randomized and blinded trials, there were 10 trials of seven days' duration or less where the safety of both drugs was directly compared. In three of these trials, the incidence of adverse events was higher with acetaminophen; there were no reported adverse events in six trials; and one trial reported a higher incidence with ibuprofen. In this subset of 10 studies, it was reported that gastrointestinal adverse events were found to be the most common type of event reported and were predominantly dyspepsia, nausea, or vomiting. None of the GI events appeared to warrant follow-up from which the author inferred there were no serious gastrointestinal events.

It was concluded: "Although we recognize that the above mentioned data are very selective and are based on information derived from a variety of trial designs and populations, it is nonetheless instructive for indicating a relatively low incidence of severe adverse reactions with both drugs when taken at their respective non-prescription dosages."

A double-blind, placebo-controlled study (N=1246) was conducted to prospectively evaluate the gastrointestinal tolerability, as compared to placebo, of the maximum nonprescription dose and duration (1200 mg/day for 10 consecutive days) of ibuprofen use in healthy subjects representative of a non-prescription analgesic user population [9]. Gastrointestinal adverse experiences were similar in the placebo and ibuprofen groups (67 out of 413, 16% with placebo vs. 161 out of 833, 19% with ibuprofen). There was no difference between the two groups in the proportion of discontinuing due to a gastrointestinal event. Gastrointestinal adverse experiences reported by ≥1% of subjects were: dyspepsia, abdominal pain, nausea, diarrhoea, flatulence, and constipation. Seventeen (1.4%) subjects had positive occult blood tests: their frequency was comparable between treatments. When used as directed to treat episodic pain, non-prescription ibuprofen at the maximum dose of 1200 mg/day for 10 days, is well-tolerated.

In two multitrial analyses [10, 11], a meta analysis [12], and a literature review [8], single doses of ibuprofen had a low incidence of gastrointestinal drug reactions, comparable to that of acetaminophen and placebo. Reports from spontaneous reporting systems in the United Kingdom [13], France and the United States [14], where a prescription is not needed for ibuprofen at a daily dose up to 1200 mg, confirm the medication's gastrointestinal safety and acceptability. A recently-completed large-scale randomized trial [15] comparing nonprescription doses of acetylsalicylic acid, acetaminophen, and ibuprofen in 8677 adults found that the rates of significant adverse reactions were: aspirin 18.7%, ibuprofen 13.7%, and acetaminophen 14.5%. Ibuprofen was not statistically different from acetaminophen. Total gastrointestinal events (including dyspepsia) and abdominal pain were less frequent with ibuprofen (4% and 2.8%, respectively) than with acetaminophen (5.3% and 3.9%) or aspirin (7.1% and 6.8%) [all $p < 0.035$]. It was concluded that "The overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol and better than that of [ASA]."

Other Ibuprofen Adverse Events

Health professionals should keep in mind other potential adverse events associated with ibuprofen use including: Crohn's disease, colitis, gastritis, hematemesis, mouth ulceration, abdominal distension, dyspepsia, abdominal pain upper, hypersensitivity, cerebrovascular accident, angioneurotic edema, dermatitis bullous, face edema, pupura, cardiac failure, myocardial infarction, angina pectoris, vertigo, visual disturbance, agranulocytosis, anemia, aplastic anemia, hematuria, interstitial nephritis, renal failure, nephrotic syndrome, proteinuria, and renal papillary necrosis, liver disorder, asthma, bronchospasm, dyspnea, wheezing, meningitis aseptic, meningitis, edema, swelling, and peripheral edema [16].

Phenylephrine

In a double-blind, crossover, placebo-controlled study of 48 patients with nasal congestion due to a common cold, where patients received 10 to 25 mg of oral phenylephrine in a single dose, the incidence of ADRs was seen to be dose-related, with higher doses having higher percentages of ADRs reported [17]. 2 ADRs were reported from patients after taking phenylephrine 10 mg, these included dry mouth and dry nose. The incidence of ADRs reported by subjects that received PE 10 mg was similar to placebo.

Health professionals should keep in mind other potential adverse events associated with phenylephrine use including: palpitations, tachycardia, increased blood pressure, hypertension, nausea, vomiting, hypersensitivity, dizziness, headache, psychomotor hyperactivity, excitability, insomnia, irritability, nervousness, restlessness, rash, and urticaria [18].

DRUG INTERACTIONS

Serious Drug Interactions

- With acetaminophen may increase the risk of adverse renal effect.
- With acetylsalicylic acid (ASA) or other nonsteroidal anti-inflammatory drugs (NSAIDs), may result in possible additive side effects (See **Contraindications**).
- With anticoagulants may increase the risk of gastrointestinal (GI) adverse events (e.g. ulceration and bleeding).

- With antihypertensives the benefit and risk must be weighed individually.
- With digoxin may increase serum digoxin concentration and the risk of digoxin toxicity.
- With diuretics may reduce the diuretic effect.
- With hypoglycaemic agents (oral agents and insulin) may increase the risk of hypoglycaemia.
- With lithium may elevate plasma lithium levels, reduce renal lithium clearance and increase the risk of lithium toxicity.
- With methotrexate may increase the risk of methotrexate toxicity.
- With monoamine oxidase inhibitors may potentiate the cardiac pressor effects of phenylephrine (See **Contraindications**).

Overview

Advil® Cold & Sinus PE is not recommended for concomitant use with any other NSAIDs, including ASA and other ibuprofen products. Documented or possible drug interactions with Advil include acetaminophen, anticoagulants (coumarin-type), antihypertensives, digoxin, diuretics, oral antidiabetic agents and insulin, lithium, methotrexate and other protein-bound drugs.

Drug-Drug Interactions

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

Acetaminophen

Although interactions have not been reported, concurrent use with Advil® Cold & Sinus PE is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs

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

α-and β-Adrenergic Blocking Agents

The vasopressor response to phenylephrine is decreased by prior administration of an α-adrenergic blocking agent such as phentolamine mesylate. Phentolamine may be used to treat hypertension if it occurs during administration of phenylephrine. Phenothiazine drugs have some α-adrenergic blocking effects; therefore, prior administration of phenothiazine may reduce the pressor effect and duration of action of phenylephrine [18].

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 [19].

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 [20, 21] 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. [22], showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two β- adrenergic blockers. Houston et al. [23] 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 [24]. As a class, the combination of an NSAID and angiotensin converting enzyme inhibitor theoretically may have the potential to decrease renal function. One study found a clinically significant decrease in renal function in 4 of 17 patients treated with hydrochlorothioazide and fosinopril who received ibuprofen 2400 mg/day for one month [25]. In contrast, Minuz [26] 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.**

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 Advil® Cold & Sinus PE to patients on anticoagulants [27, 28].

Cough-cold/allergy Medications
The use of other decongestants, cough and cold medications, allergy medications or medications containing phenylephrine 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 [29].

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. Administration of furosemide or other diuretics may decrease arterial responsiveness to vasopressors such as phenylephrine [18].

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
Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur [1].

Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers [30]. 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 [31]. 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 and Drugs Affecting Norepinephrine
The cardiac and pressor effects of phenylephrine are potentiated by prior administration of monoamine oxidase inhibitors (MAOIs) because the metabolism of phenylephrine is reduced. The potentiation is greater following oral administration of phenylephrine than after parenteral administration of the drug because reduction of the metabolism of phenylephrine in the intestine results in increased absorption of the drug. Oral administration of phenylephrine to patients receiving a MAOI should be avoided [18] (*See Contraindications*).

Tricyclic antidepressants (e.g., imipramine) or guanethidine may also potentiate the vasopressor effects of phenylephrine [18].

Advil® Cold & Sinus PE 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 phenylephrine or other sympathomimetic drugs such as ephedrine in combination with or shortly after discontinuing MAO inhibitors [18] (See **Contraindications**).

Oxytocic Drugs
When a vasopressor is used in conjunction with oxytocic drugs, the pressor effect is potentiated [18].

Sympathomimetic Agents
Combination products containing phenylephrine and a bronchodilator sympathomimetic agent should not be used concomitantly with epinephrine or other sympathomimetic agents because tachyardia or other serious arrhythmias may occur [18].

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

Atropine sulfate blocks the reflex bradycardia caused by phenylephrine and enhances the pressor response to phenylephrine.

An excessive rise in blood pressure may occur if phenylephrine is administered to patients receiving a parenteral injection of an ergot alkaloid such as ergonovine maleate. The possibility that digitalis can sensitize the myocardium to the effects of sympathomimetic drugs should be considered.

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

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

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

Drug-Lifestyle Interactions
Avoid drinking alcohol while taking Advil® Cold & Sinus PE, as this may increase the risk of serious stomach bleeding. Avoid smoking while taking Advil® Cold & Sinus PE or other NSAIDS.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Advil® Cold & Sinus PE should not be used for more than 3 days for a fever or 5 days for pain/cold symptoms.

Recommended Dose and Dosage Adjustment

Adults under 65 years of age and Children over 12 years of age: Take 2 caplets every 4 hours as needed with or without food. Do not exceed 6 caplets in 24 hours, unless directed by a physician.

Take with food or milk if stomach upset occurs.

Missed Dose

Continue to take this product according to the directions as needed, after a missed dose. Do not take twice the recommended dose following a missed dose [32].

Administration

See **Recommended Dose and Dosage Adjustment**.

OVERDOSAGE

Signs and Symptoms of Overdose

Ibuprofen

The toxicity of ibuprofen overdose is dependent upon the amount of drug ingested and the time elapsed since ingestion; individual responses may vary, thus making it necessary to evaluate each case separately. Although uncommon, serious toxicity and death have been reported with ibuprofen overdosage. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy, vertigo, drowsiness (somnolence), dizziness and insomnia. Other central nervous system (CNS) symptoms include headache, loss of consciousness, tinnitus, CNS depression, convulsions and seizures. Metabolic acidosis, abnormal hepatic function, hyperkalemia, renal failure, dyspnea, respiratory depressions and apnoea (primarily in very young pediatric patients) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation, also have been reported [33-35].

Phenylephrine Hydrochloride

Overdosage of phenylephrine may cause hypertension, headache, seizures, cerebral hemorrhage, palpitation, paresthesia, or vomiting. Headache may be a symptom of hypertension. Hypertension may be relieved by administration of an α-adrenergic blocking agent (e.g., phentalomine) [18].

Other overdose symptoms include: bradycardia, palpitations, tachycardia, nausea, dizziness, tremor, anxiety, irritability, nervousness, restlessness, insomnia, convulsion and increased blood

pressure [18]. Phenylephrine overdose may also cause hypersensitivity, psychomotor hyperactivity, excitability, rash, and uticaria.

Treatment of Overdosage

In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Emesis is most effective if initiated within 30 minutes of ingestion. Orally administered activated charcoal may help in reducing the absorption of the drug 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 [36]. Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. Management of hypotension, acidosis and gastrointestinal bleeding may be necessary.

Physicians should contact the Regional Poison Control Centre for additional guidance about overdose management.

Examples of Ibuprofen Overdose
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.

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 [37].

With electrolyte replacement and other intensive measures, a 21-month-old child recovered within 5 days after accidental ingestion of 8 g of ibuprofen [38].

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 [39].

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 [40].

Examples of Phenylephrine Overdose
A 33-year-old woman experienced hypertension, bradycardia, an extremely severe headache and slightly blurred vision after receiving 750ug of intravenous phenylephrine. She was treated with hydralazine 20 mg intravenously followed by intravenous phentolamine 5 + 5 mg, which subsided the headache and decreased the blood pressure. The headache persisted in a mild form, together with blurred vision for a further 6 hours [41].

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ibuprofen

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects as a non-steroidal anti-inflammatory drug are thought to result from its inhibitory effect on the enzyme cyclo-oxygenase, which results in a marked reduction in prostaglandin synthesis [16].

Ibuprofen, like all nonsteroidal anti-inflammatory drugs (NSAIDs), is an analgesic, antipyretic, and anti-inflammatory medication [42] There is strong evidence to support the view that the main mechanism of action of ibuprofen (like other NSAIDs) is related to decreasing prostaglandin biosynthesis [43].

Prostaglandins are naturally-occurring fatty acid derivatives that are widely distributed in the tissues. They are believed to be a common factor in the production of pain, fever, and inflammation. Prostaglandins are believed to sensitize tissues to pain- and inflammation-producing mediators such as histamine, 5-hydroxytryptamine, and kinins. The enzyme catalysing the committed step in prostaglandin biosynthesis is prostaglandin endoperoxide synthase, also known as cyclooxygenase. There is significant evidence that the main mechanism of analgesic/antipyretic action of NSAIDs is prostaglandin biosynthesis inhibition [44]. Other pharmacologic effects such as lysosome and plasma membrane stabilization have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

A recent study confirmed that ibuprofen 400 mg provided a significantly faster onset of relief as measured by first perceptible relief, meaningful relief, per cent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache [45].

Phenylephrine Hydrochloride

Phenylephrine acts predominantly by a direct effect on α-adrenergic receptors. It has predominantly alpha adrenergic activity and is without stimulating effects on the central nervous system. The sympathomimetic effect of phenylephrine produces vasoconstriction, which in turn relieves nasal congestion.

In therapeutic doses, the drug has no substantial stimulant effect on the β-adrenergic receptors of the heart (β_1-adrenergic receptors) but substantial activation of these receptors may occur when larger doses are given. Phenylephrine does not stimulate β-adrenergic receptors of the bronchi or peripheral blood vessels (β_2-adrenergic receptors). It is believed that α-adrenergic effects result from the inhibition of the production of cyclic adenosine-3′,5′-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas β-adrenergic effects result from stimulation of adenyl cyclase activity. Phenylephrine also has an indirect effect by releasing norepinephrine from its storage sites. Although the manufacturer reports that there is no decrease in effectiveness with repeated injections of phenylephrine, some investigators have reported that tachyphylaxis may develop. The main effect of therapeutic doses of phenylephrine is vasoconstriction [18].

Pharmacodynamics

Ibuprofen
Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory, analgesic and antipyretic activity. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition. After absorption of the racemic ibuprofen, the [-]R-enantiomer undergoes interconversion to the [+]S-form. The biological activities of ibuprofen are associated with the [+]S-enantiomer.

Phenylephrine Hydrochloride
Phenylephrine is a powerful vasoconstrictor. It is used as a nasal decongestant and cardiotonic agent. Phenylephrine is a postsynaptic α_1-receptor agonist with little effect on β-receptors of the heart. Vasoconstriction in the mucosa of the respiratory tract leads to decreased edema and increased drainage of sinus cavities.

Pharmacokinetics

Absorption:

Ibuprofen
Ibuprofen is rapidly and almost completely absorbed. Peak serum concentration occurs within 1-2 hours in adults [46]. In febrile children ages 3 months to < 12 years, the time of peak serum concentration was 1.60 and 1.54 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively [47]. Nahata [48] found a time to peak concentration of 1.1 and 1.2 hours for these respective doses. A similar study in febrile children by Walson [49] which used an ibuprofen suspension showed a time of peak serum concentration of 1.3 and 1.7 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively. Walson also found that mean ibuprofen plasma concentration at one hour was 21.7 ± 6.7, and 28.4 ± 15.2 µg/mL for 5 mg/kg and 10 mg/kg, respectively. Food decreases the rate but not the extent of absorption [46].

Phenylephrine Hydrochloride
Following oral administration, nasal decongestion may occur within 15 or 20 minutes and may persist for 2-4 hours [18]. Phenylephrine is readily and completely absorbed after oral administration. Peak concentrations are reached between 0.75 and 2 hours after administration [50].

Distribution:

Ibuprofen
The volume of distribution in adults after oral administration is 0.1-0.2 L/kg [51]. In febrile children, the volume of distribution is 0.18 and 0.22 L/kg for ibuprofen 5 mg/kg and 10 mg/kg, respectively [47].

At therapeutic concentrations, ibuprofen is highly bound to whole human plasma and to site II of purified albumin [51]. There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses [46].

Phenylephrine Hydrochloride
No data exist on the extent of protein binding. Penetration into the brain appears to be minimal [50]. The distribution half-life is 5 minutes [52]. Human distribution data indicate that the apparent volume of distribution is >40 L [52]. It is not known whether phenylephrine is distributed into milk [18].

Metabolism:

Ibuprofen
Ibuprofen is a racemic mixture of R-(-) ibuprofen and S-(+) ibuprofen. R-(-) ibuprofen undergoes extensive enantiomeric conversion to S-(+) ibuprofen in humans, averaging between 53% and 65%.[9] S-(+) ibuprofen is believed to be the pharmacologically more active enantiomer. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl] propionic acid and 2-[4-(2-hydroxy-2-methylpropyl]propionic acid, have been identified in plasma and urine [53]. The metabolites 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been found in urine in very small concentrations [54, 55]. Cytochrome P450 (CYP) 2C9 has been identified as the most important catalyst for formation of all oxidative metabolites of R-(-) and S-(+) ibuprofen [56]. Approximately 80% of a dose is recovered in urine, primarily as carboxymetabolites and conjugated hydroxymetabolites [51]. Ibuprofen does not appear to induce the formation of drug metabolizing enzymes in the rat [53].

Phenylephrine Hydrochloride
Phenylephrine undergoes extensive biotransformation in the intestinal wall and in the liver, which accounts for the bioavailability of only 38% after oral administration [50, 52]. The principal routes of metabolism are the sulfate conjugates, which are formed largely in the gut wall, and oxidative deamination by monoamine oxidase [50, 57, 58]. Some glucuronidation of phenylephrine also occurs [50].

Excretion:

Ibuprofen
Ibuprofen's plasma half-life in adults is 1.5-2.0 hours [59]. In febrile children, the plasma half-life is 1.65 and 1.48 hours for ibuprofen 5 mg/kg and 10 mg/kg, respectively [47]. Parent drug and metabolites are primarily excreted in the urine; bile and faeces are relatively minor elimination routes. Total recovery in urine is between 70% and 90% of the administered dose within 24 hours [51].

There is no evidence of a differential metabolism or elimination of ibuprofen in the elderly. A pharmacokinetic evaluation of ibuprofen in geriatric subjects (65 to 78 years) compared with young adult subjects (22 to 35 years) found that there was no clinically significant difference in the kinetic profiles of ibuprofen for these age groups [60]. Furthermore, there was no statistically significant difference between the two populations in the urinary excretion pattern of the drug and its major metabolites.

The pharmacokinetics of ibuprofen have also been evaluated in children, in whom the metabolism has been shown to be similar to that reported for adults. Walson reported that for ibuprofen 10 mg/kg given to children under 12 years of age, peak plasma concentration occurred at 1.5 hours and then declined with a plasma half-life of 1.8 hours [61]. Thus, ibuprofen appears to exhibit a similar pharmacokinetic profile in all age groups examined.

Phenylephrine Hydrochloride
Phenylephrine and its metabolites are excreted unchanged almost entirely in the urine. Only 2.6% of the drug is excreted unchanged after oral administration [50, 52]. The elimination half-life of phenylephrine after oral administration is approximately 3.4 hours [50, 52]. Average total clearance has been estimated as 2095 ml/minute (125.7L/hr) [50].

Special Populations and Conditions

Breast Milk and Placental Transport
Ibuprofen excretion in breast milk following ingestion of one 400 mg ibuprofen tablet every 6 hours for five doses was below the level (i.e., 1µg/mL) of detection [62]. However, a later study using a more sensitive assay showed ibuprofen to be rapidly excreted in breast milk 30 minutes following oral ingestion of 400 mg of ibuprofen at a concentration of 13 ng/mL. A milk:plasma ratio of 1:126 was determined and the exposure of a suckling infant was calculated to be approximately 0.0008% of the maternal dose [63].

Phenylephrine does not appear to be distributed to any great extent into breast milk. Advil® Cold & Sinus PE should not be used by pregnant or nursing mothers.

STORAGE AND STABILITY

Advil® Cold & Sinus PE caplets should be stored in tightly-closed containers under room temperature (15-30ºC) and protected from moisture and excessive heat.

SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Advil® Cold & Sinus PE
Each Advil® Cold & Sinus PE caplet contains 200 mg ibuprofen and 5 mg phenylephrine hydrochloride. Advil® Cold & Sinus PE caplets are available in blisters of 10, bottles of 40 and 72 and pouches of 2.

Non medicinal ingredients:
acesulfame potassium, carboxymethylcellulose sodium, corn starch, croscarmellose sodium, dextrose monohydrate, flavour, hypromellose, iron oxides, lecithin, maltodextrin, medium chain triglycerides, microcrystalline cellulose, pharmaceutical ink, polydextrose, pregelatinized starch,

silicon dioxide, sodium lauryl sulfate, stearic acid, sucralose, talc, titanium dioxide, xanthan gum.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Ibuprofen

Proper name: Ibuprofen

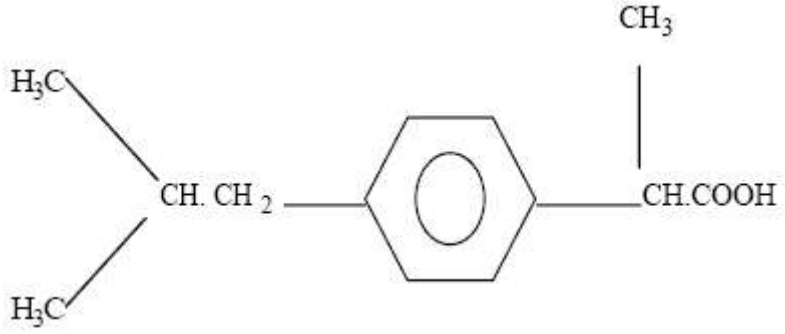
Chemical name: α-methyl-4-(2-methylpropyl)benzeneacetic acid

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

Molecular formula: $C_{13}H_{18}0_2$

Molecular mass: 206.28 Daltons

Structural formula:



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

Solubilities: 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 and pH values: pKa : 4.43
pH : 4.6 - 6.0, in a solution of 1 in 20.

Melting Point: 75 – 78°C

Phenylephrine Hydrochloride

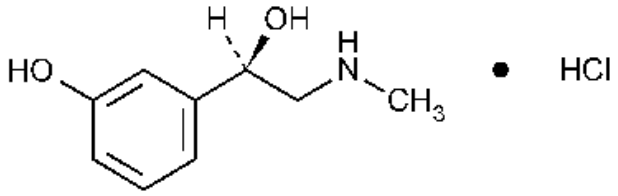
Proper name: phenylephrine hydrochloride

Chemical name: R-3 hydroxy-alpha-((methylamino)
-methyl)benzynemethanolhydrochloride

Molecular formula: $C_9H_{14}ClN0_2$;

Molecular mass: 203.6681

Structural formula:



Physical Characteristics: Odorless, white or practically white crystals having a bitter taste.

Solubilities: Freely soluble in water and in alcohol.

pKa and pH values: pK_{a1} = 8.9 (phenole)
pK_{a2} = 10.1 (secondary amine)
pH (1% aqueous solution) = 5

Melting Point: 140-145°C

CLINICAL TRIALS

Comparative Bioavailability Studies

In a three-way crossover, open-label, single-dose, fasting, bioequivalence study conducted with normal, healthy, non-smoking male and female subjects (N=21 for ibuprofen; N=23 for phenylephrine), Advil® Cold & Sinus PE (ibuprofen/phenylephrine hydrochloride) 200 mg/5 mg caplets (Pfizer Consumer Healthcare, a division of Pfizer Canada Inc.) were compared to Motrin® IB (ibuprofen) 200 mg tablets (McNeil Consumer Healthcare, Division of Johnson and Johnson Inc.) and Sudafed® PE Extra Strength (phenylephrine hydrochloride) 10 mg Tablets (McNeil Consumer Healthcare, Division of Johnson & Johnson Inc.) [7]. The pharmacokinetic and statistical data for the two drugs are summarized in Tables 1 and 2.

Table 1
Summary Table of the Comparative Bioavailability Data

Ibuprofen
(2 x 200 mg ibuprofen/5 mg phenylephrine hydrochloride or 2 x 200 mg ibuprofen)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (μg·hr/mL)	121.85 123.91 (19.14)	121.71 123.70 (19.27)	100.83	97.55-104.23
AUC_I (μg·hr/mL)	124.36 126.48 (19.17)	124.15 126.26 (19.70)	100.96	97.67-104.35
C_{max} (μg/mL)	36.45 37.17 (19.78)	37.44 38.03 (17.16)	99.18	90.38-108.84
T_{max} (h) δ	1.75 (0.50 - 3.00)	1.13 (0.50 - 2.50)		
$T_{½}$ (h) +	1.99 (15.65)	2.00 (13.18)		

*Advil® Cold & Sinus PE caplets (ibuprofen/phenylephrine hydrochloride) 200 mg/5 mg caplets (Pfizer Consumer Healthcare, a division of Pfizer Canada Inc., Canada).
† Motrin® IB (ibuprofen) 200 mg Tablets (McNeil Consumer Healthcare, Division of Johnson & Johnson Inc., Canada).
δ Expressed as median (range) only.
+ Expressed as mean (CV%) only.

Table 2

Summary Table of the Comparative Bioavailability Data

Phenylephrine + Conjugates
(2 x 200 mg ibuprofen/5 mg phenylephrine hydrochloride or 1 x 10 mg phenylephrine hydrochloride)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·hr/mL)	428.16 448.68 (31.08)	425.98 450.31 (33.84)	101.36%	96.71-106.24
AUC_I (ng·hr/mL)	446.44 466.18 (29.82)	444.40 467.46 (32.32)	101.25%	96.97-105.72
C_{max} (ng/mL)	138.49 148.53 (37.73)	145.14 155.08 (37.89)	96.92%	90.44-103.87
T_{max} (h) δ	1.27 (0.75 - 3.00)	1.00 (0.50 - 1.50)		
$T_{½}$ (h) +	1.86 (17.79)	1.92 (15.33)		

*Advil® Cold & Sinus PE caplets (ibuprofen/phenylephrine hydrochloride) 200 mg/5 mg caplets (Pfizer Consumer Healthcare, a division of Pfizer Canada Inc., Canada).
† Sudafed® PE Extra Strength (phenylephrine hydrochloride) 10 mg Tablets (McNeil Consumer Healthcare, Division of Johnson & Johnson Inc., Canada).
δ Expressed as median (range) only.
+ Expressed as mean (CV%) only.

Published Literature (Adults >12 years of age)

Ibuprofen

There is considerable evidence in the world literature documenting the efficacy of 200 to 400 mg doses of ibuprofen in the treatment of mild to moderate pain in a broad range of pain models.

Sore Throat Pain

A double-blind, randomized study showed that ibuprofen 400 mg relieved sore throat pain significantly better than placebo and acetaminophen [64].

Headache

A double-blind, randomized study showed that ibuprofen 400 mg relieved headache pain significantly better than acetaminophen 1000 mg and placebo [65]. Another double-blind, placebo-controlled, randomized study showed that ibuprofen 400 mg began to exert a significant analgesic effect on headache within 30 minutes after dosing [66].

Dental Pain

A double-blind, randomized study showed that ibuprofen 400 mg relieved dental pain following removal of impacted third molars significantly better than acetaminophen and placebo [67]. Several other comparative dental studies have described similar results [68-74].

Muscle Aches
A double-blind, randomized study showed that ibuprofen 400 mg every four hours for a total of three doses relieved muscle soreness following exercise significantly better than acetaminophen 1000 mg and placebo every four hours [75].

Dysmenorrhea
Several studies demonstrate the significant effect of ibuprofen compared to placebo or other active analgesics on uterine pain and cramping [76-81].

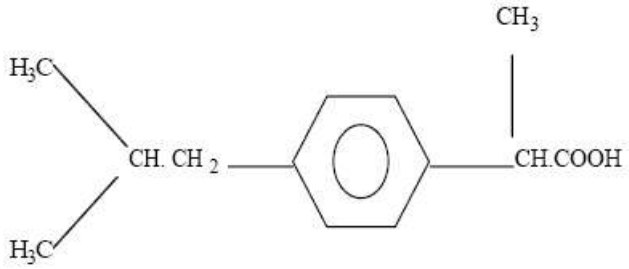
Fever
Multiple studies in the archival literature using ibuprofen does range from 5 to 10 mg/kg have shown the drug's ability to lower fever in children [82-105].

Phenylephrine Hydrochloride
In a double-blind, crossover, placebo-controlled study of 48 healthy adult patients with nasal congestion due to a common cold, oral phenylephrine significantly improved nasal airway flow. Patients received 10, 15 or 25 milligrams (mg) oral phenylephrine as a single dose. Mean nasal airflow and resistance were measured at baseline and following medication and patients subjectively evaluated improvement. Statistically significant differences were observed for mean nasal airflow and resistance for the three comparisons of phenylephrine with placebo. Subjective estimates of improvement after phenylephrine were superior to placebo effects for all three doses. Peak effectiveness was observed between 30 and 90 minutes [17].

DETAILED PHARMACOLOGY

Structural Formula and Chemistry

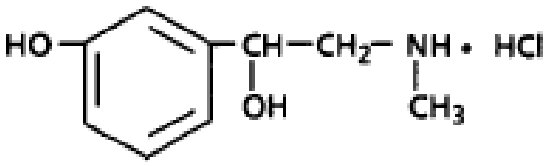
Ibuprofen
Chemically, ibuprofen is described as 2-(4-isobutylphenyl) propionic acid with the following structural formula:



Ibuprofen is a white crystalline solid with a slight odour and taste. It is non-hygroscopic and has a low solubility in water. The compound is readily soluble in organic solvents and aqueous alkalis. In the dry state, it is physically and chemically stable. It has a melting point of about 75°C.

Phenylephrine Hydrochloride

Chemically, phenylephrine is described as R-3 hydroxy-alpha-((methylamino)-methyl)benzynemethanolhydrochloride with the following structural formula:



Phenylephrine is a sympathomimetic vasoconstrictor that is closely related to adrenaline in structure. Phenylephrine differs chemically from adrenaline only in the absence of one hydroxyl group from the benzene ring. Phenylephrine contains a single chiral carbon atom and thus exists as an enantiomeric pair of stereoismers. It is used commercially as the (-)-enantiomer as phenylephrine hydrochloride [57].

Animal Pharmacology

Ibuprofen

After single oral doses of 20 to 150 mg/kg of C^{14} labelled ibuprofen rats, the peak plasma level occurred at or before the earliest time examined (20 minutes in the 20 mg/kg group and 45 minutes in the 150 mg/kg group) and peak levels occurred with 45 minutes of dosing in nearly all tissues examined. The concentration in plasma and tissue decreased to very low levels by six hours after the 20 mg/kg dose and by 17 hours after the 150 mg/kg dose. Sixteen to 38% of the daily dose of ibuprofen was excreted in the urine [106].

A similar dose was given to dogs for periods of up to six months with no evidence of accumulation of the drug or its metabolites [106].

Inhibition of Platelet Aggregation in Animals:

Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated by preventing platelet disposition in aortopulmonary arterial bypass grafts in the dog [107]. The drug's protective action against fatal pulmonary embolism in rabbits injected intravenously with arachidonic acid may also relate to platelet inhibition [108, 109]. Various prostaglandins and thromboxane A_2 (TXA_2), are important factors in normal platelet aggregation. Cyclooxygenase inhibition reduces TXA_2 production and release, thereby reducing platelet aggregation [110]. Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation [111], but it is not known to what extent TXA_2 synthesis inhibition is involved in this effect.

Phenylephrine Hydrochloride

When male Wistar rats were given intraperitoneal injections of titrated phenylephrine, 72% of the label was collected in the urine within 24 hours. Sixteen percent of the dose was unconjugated phenylephrine, the sulfate conjugate, or the glucuronide conjugate, and approximately 56% of the dose was found as *meta*-hydroxymanelic acid (6%), *meta*-hydroxyphenylglycol (50%), or their sulfate or glucuronide conjugates [112].

Human Pharmacology

Ibuprofen

Two metabolites of ibuprofen were isolated from the urine of patients who had been treated for one month with the drug. The metabolites were identified at 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine [106].

Phenylephrine Hydrochloride

Phenylephrine acts predominantly by a direct effect on α-adrenergic receptors. In therapeutic doses, the drug has no substantial stimulant effect on the β-adrenergic receptors of the heart (β_1-adrenergic receptors) but substantial activation of these receptors may occur when larger doses are given. Phenylephrine does not stimulate β-adrenergic receptors of the bronchi or peripheral blood vessels (β_2-adrenergic receptors). It is believed that α-adrenergic effects result from the inhibition of the production of cyclic adenosine-3',5'-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas β-adrenergic effects result from stimulation of adenyl cyclase activity. Phenylephrine also has an indirect effect by releasing norepinephrine from its storage sites [18].

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

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

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

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Ibuprofen

Single Dose Toxicity Studies

Single dose toxicity studies have been conducted using mice, rats, and dogs [106].

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

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

Acute signs of poisoning were prostration in mice, and sedation, prostration, loss of righting reflex and laboured respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration.

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

Multiple Dose Studies

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

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

The above experiment was adapted to establish whether the effects of ibuprofen treatment on rats were reversible when dosing ended [106]. In this instance, rats were administered 180, 60, or 20 mg/kg/day ibuprofen for 13 weeks instead of 26 weeks, whereupon half the animals in each group were sacrificed and the remaining rats were maintained, undosed, for three weeks and then sacrificed. Haematological examinations were performed after 4, 8, and 12 weeks of treatment.

Results obtained from the dosing phase of this 13-week experiment reflected the results obtained previously, where rats were dosed for 26 weeks. Males receiving 180 mg/kg/day had enlarged kidneys, spleen, and testes; while those on lower doses had normal organ weights. Females on all three doses had enlarged kidneys, the extent of which was dose-dependent. Enlargement of the liver and ovaries was observed in females receiving 180 mg/kg/day, and of the spleen and ovaries on those on 60 mg/kg/day. None of the enlarged organs were histologically abnormal. Three weeks following withdrawal of treatment, the organ to body weight ratios had completely or almost completely returned to normal. Rats receiving 180 mg/kg/day were anaemic from week 4 of dosing and when examined after the final dose, were found to have intestinal 31 lesions. These effects were not seen at the lower doses, thereby confirming the results of the first experiment. Since the highest dose of 180 mg/kg/day was only moderately toxic, an additional group of rats was dosed with 540 mg/kg/day [106]. All these rats died or were killed *in extremis* after 4 days' dosing. All had intestinal ulceration with peritonitis, and some also had slight renal tubular dilation.

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

Carcinogenic Potential

Thirty male and 30 female rats were given 180 mg/kg/day of ibuprofen orally for 55 weeks and 60 mg/kg/day for the next 60 weeks. The only specific pathological effect observed was intestinal ulceration. There was no evidence of tumour induction and it is concluded that ibuprofen is not carcinogenic in the rat [113].

Teratology Study in Rabbits

New Zealand white rabbits were given 0, 7.5, 20 and 60 mg/kg daily of ibuprofen from day 1 to day 29 of pregnancy. The mean foetal weight was unaffected; litter size was unaffected at the lower doses. Congenital malformations did occur in both treated and untreated groups with no consistent pattern except for one litter of 4 young with cylcopia. The results of this experiment indicate that ibuprofen is not teratogenic when given in toxic doses to rabbits [106].

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 [106].

Penetration of Ibuprofen into the Rabbit and Rat Foetus

Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C^{14} labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and foetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and foetus indicating that the drug and its metabolites readily crossed the placental barrier into the foetal circulation [106].

Phenylephrine Hydrochloride

LD_{50} values (mg/kg body weight) have been determined in several species by various routes of administration [112] as shown in the following table:

Dogs	Intraperitoneal	16
Mice	Oral	120
	Intraperitoneal	89
	Subcutaneous	22
	Intravenous	0.112
Wistar Rats	Intraperitoneal	33
	Subcutaneous	17
Rats (strain unknown)	Oral	350
	Intraperitoneal	65
	Subcutaneous	92
	Intravenous	0.44
Rabbits	Intravenous	0.5
	Intramuscular	7.2
	Subcutaneous	22

Phenylephrine given to pregnant rabbits during the last third gestation produced fetal growth retardation and the onset of early labour [112].

In National Toxicology Program studies, phenylephrine hydrochloride was not mutagenic in bacteria (*Salmonella tryphimurium*) with or without metabolic activation. The evidence for mutagenicity was equivocal in mammalian cells without metabolic activation at nearly toxic doses, and phenylephrine hydrochloride induced Sister-chromatid exchanges in mammalian cells in the absence of metabolic activation [112].

Under the conditions of a National Toxicology Program two-year study, there was no evidence of phenylephrine hydrochloride carcinogenicity for male or female F344/N rats given 620 or 1250 ppm in feed or for male or female B6C3F1 mice given 1,200 or 2500 ppm in feed. Survival of high dose males was greater than that of controls, and the incidences of mononuclear cell leukemia and pheochromocytomas were lower in dosed than in control male rats [114].

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PART III: CONSUMER INFORMATION

ADVIL® COLD & SINUS PE
(Ibuprofen and Phenylephrine Hydrochloride Caplets)

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

ABOUT THIS MEDICATION

What the medication is used for:
Advil® Cold & Sinus PE provides fast, effective, temporary relief of symptoms associated with the common cold including nasal congestion, headache, fever, sinus pain, and minor body aches and pains.

What it does:
Advil® (ibuprofen) reduces pain and fever. Phenylephrine hydrochloride is a nasal decongestant.

When it should not be used:

Do not take Advil® Cold & Sinus PE if you have or are:

- allergic/hypersensitive to acetylsalicylic acid (ASA), ibuprofen, other salicylates, other non-steroidal anti-inflammatory drugs (NSAIDs), phenylephrine hydrochloride or other sympathomimetic amines or any ingredient in the formulation or component of the container (Refer to the nonmedicinal ingredients section of this insert),
- active peptic ulcer, a history of recurrent ulceration or active gastrointestinal bleeding,
- taking a monoamine oxidase inhibitor (MAOI) 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), uticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake,
- been diagnosed with severe high blood pressure or have heart disease,
- about to have or just had heart surgery,
- serious liver disease,
- severe kidney disease,
- inflammatory bowel disease such as ulcerative colitis or Crohn's disease,
- Raynaud's Syndrome (a disorder of the circulatory system),
- Sytemic Lupus Erythematosus,
- pregnant or nursing.

What the medicinal ingredients are:
Ibuprofen and phenylephrine hydrochloride.

What the important non medicinal ingredients are:
acesulfame potassium, carboxymethylcellulose sodium, corn starch, croscarmellose sodium, dextrose monohydrate, flavour, hypromellose, iron oxides, lecithin, maltodextrin, medium chain triglycerides, microcrystalline cellulose, pharmaceutical ink, polydextrose, pregelatinized starch, silicon dioxide, sodium lauryl sulfate, stearic acid, sucralose, talc, titanium dioxide and xanthan gum.

What dosage forms it comes in:
Advil® Cold & Sinus PE caplets contain 200 mg ibuprofen and phenylephrine hydrochloride 5 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Caution in patients at risk of gastrointestinal tract irritation,**
- **Patients at risk of kidney problems, including the elderly or those using diuretics.**
- **Stop use immediately if you have difficulty or pain when urinating.**

BEFORE you use Advil® Cold & Sinus PE, talk to your doctor or pharmacist if you have or have had any of the following:

- blood clotting disorder (such as hemophilia)
- breathing problems or chronic lung disease (such as chronic bronchitis)
- diabetes,
- depression,
- itchy skin or hives
- high blood pressure
- history of gastrointestinal illness
- difficulty in urination due to enlargement of the prostate gland,
- glaucoma
- mild to moderate kidney disease
- mild to moderate liver disease
- thyroid disease,
- any other serious disease, are under doctor's care for

any serious condition, or are taking any other drug including nonprescription (over the counter) drugs.

Do not use for longer than 3 days for a fever or for 5 days for pain/cold symptoms.

INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking:

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

Before you use Advil® Cold & Sinus PE, talk to your doctor or pharmacist if you are taking any other drug, especially:

- Acetaminophen
- Acetylsalicylic acid (ASA)
- Allergy medications
- Anticoagulants (blood thinning medications)
- Antidepressants
- Anti-hypertensives (blood pressure medications)
- Antibiotics (levofloxacin)
- Asthma medications (sympathomimetic agents)
- Benzodiazapenes
- Cold medications
- Cyclosporine
- Diabetes medication (including insulin and oral antidiabetic agents)
- Digoxin
- Diuretics (water pills)
- Epinephrine or norepinephrine
- Glucocorticoids (oral steroids)
- Lithium
- Methotrexate
- Monoamine Oxidase Inhibitors
- Nonsteroidal anti-inflammatory drugs (NSAIDs); including naproxen and ibuprofen
- Phenytoin
- Probenecid
- Thyroxine

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

Do not smoke or drink alcohol while using this product.

PROPER USE OF THIS MEDICATION

Usual dose:

Adults 65 and under and Children over 12 years: Take 2 caplets every 4 hours as needed. Do not exceed six caplets in 24 hours, unless directed by a physician.

Children 12 years and under: Do not use.

Take with food or milk if stomach upset occurs.

Stop use and call your doctor if fever persists for more than 3 days or pain/cold symptoms last for more than 5 days.

Overdose:

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

Missed Dose:

Continue to take this product according to the directions as needed, after a missed dose. Do not take twice the recommended dose following a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Advil® Cold & Sinus PE may occasionally produce unwanted side effects, such as heartburn, constipation, nausea, bloating, nervousness or sleeplessness.

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

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

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Uncommon	Symptoms of allergic reaction, including: rash, severe itching/ redness, blisters, swelling, or trouble breathing			T
	Blood in vomit, bloody or black stools			T
	Abdominal pain, vomiting, diarrhea		T	
	Ringing or buzzing in the ears / dizziness		T	
	Change in vision,		T	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect		**Talk with your doctor or pharmacist**	**Seek immediate emergency**
	Fluid retention	**T**	

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

This is NOT a complete list of side effects. For any unexpected effects while taking Advil® Cold & Sinus PE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°-30°C). Protect from moisture and excessive heat.

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

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor,
GlaxoSmithKline Consumer Healthcare Inc.
, Mississauga, ON L5N 6L4at: 1-888-275-9938 or www.advil.ca.

This leaflet was prepared by
GlaxoSmithKline Consumer Healthcare Inc.

Product monograph available to physicians and pharmacists upon request.

Last revised: 06-July-2020