

PRODUCT MONOGRAPH

**ADVIL COLD & FLU  
ADVIL PAIN & HEAD COLD NIGHT**

Ibuprofen and Diphenhydramine Citrate Caplets  
200 mg/38 mg

Analgesic/Antipyretic and Antihistamine

Pfizer Consumer Healthcare, a division of Pfizer Canada  
ULC  
450-55 Standish Court  
Mississauga, Ontario  
Canada L5R 4B2

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**ADVIL COLD & FLU  
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Ibuprofen and Diphenhydramine Citrate Caplets

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Caplet: ibuprofen 200 mg, diphenhydramine citrate 38 mg	None. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

**INDICATIONS AND CLINICAL USE**

Advil® Cold & Flu and Advil® Pain & Head Cold Night (ibuprofen and diphenhydramine citrate caplets) are indicated for the relief of cold and influenza symptoms including: Body aches and pains, sore throat pain, fever, headache, runny nose, sneezing and itchy watery eyes.

**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 & Flu or Advil® Pain & Head Cold Night in this population is not recommended. (See *Warnings and Precautions, Special Populations, Geriatrics*) [138].

**Pediatrics (<16 years of age):**

Advil® Cold & Flu and Advil® Pain & Head Cold Night are not indicated for children <16 years of age.

**CONTRAINDICATIONS**

- Ibuprofen is contraindicated for patients with active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system [135].
- Both ibuprofen and diphenhydramine have been associated with hypersensitivity. Patients who are hypersensitive to these drugs or to any ingredient in the formulation or component of the container should not use this product. For a complete listing, see *Dosage Forms, Composition and Packaging* Section of the product monograph. The potential for cross-reactivity between different NSAIDs must be kept in mind [136].

- Ibuprofen containing products should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects [135].
- 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.
- Advil® Cold & Flu and Advil® Pain & Head Cold Night are not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.
- Children 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.
- Ibuprofen is contraindicated in patients with systemic lupus erythematosus, as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.
- Ibuprofen should not be used in the presence of known hyperkalemia (also see Warnings and Precautions - Renal section).
- Advil® Cold & Flu and Advil® Pain & Head Cold Night should not be used during the last 3 months of pregnancy [17], or by Nursing Mothers.
- Ibuprofen should not be used right before or after heart surgery.
- Children and adolescents (see Indications)

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

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

## **General**

As with other anti-inflammatory drugs, ibuprofen may mask the usual signs of infection [135].

Ibuprofen is NOT recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions. (See **Drug Interactions – Drug/Drug Interactions – Acetylsalicylic acid (ASA) or other NSAIDs**)

Patients with glaucoma, chronic lung disease (asthma, emphysema or chronic bronchitis), or difficulty in urination due to prostate enlargement or bladder neck problems should not take this product unless directed by a physician [126].

If symptoms of fever and pain associated with flu symptoms of itchy/watery eyes and runny nose do not improve within 5 days, patients should stop use and consult a physician [126].

## **Carcinogenesis and Mutagenesis**

Not applicable.

## **Cardiovascular**

Ibuprofen: use of ibuprofen may precipitate congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations [135].

Long term continuous use may increase the risk of heart attack or stroke [146].

Diphenhydramine: Vasconstrictive effects have been noted [17].

## **Dependence/Tolerance**

A combination of butorphanol and diphenhydramine is being increasingly used as a drug of abuse. Diphenhydramine dependence has been documented in case reports involving mentally ill patients [17].

## **Ear/Nose/Throat**

Patients with complete or partial syndrome of nasal polyps should not use this drug. (See *CONTRAINDICATIONS*).

## **Endocrine and Metabolism**

Patients with thyroid disease should not take this drug unless directed by a physician [136].

## **Fluid and Electrolyte Balance** [135]

Fluid retention and oedema have been observed in patients treated with ibuprofen. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Advil® Cold & Flu and Advil® Pain & Head Cold Night caplets 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** [135]

Serious gastrointestinal (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 NSAIDs, 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 & Flu and Advil® Pain & Head Cold Night caplets should be given under close medical supervision to patients prone to GI 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 GI 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 & Flu and Advil® Pain & Head Cold Night caplets should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. The major risk factors are a prior history of serious GI events and increasing age. Possible risk factors include other factors such as *Helicobacter pylori* infection, excess alcohol intake, smoking, female gender and concomitant oral steroid and anticoagulant use. Anti-coagulants, anti-platelet agents (including ASA) or selective serotonin reuptake inhibitors

(SSRI's) have been associated with increased risk. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

Diphenhydramine may cause epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation [16].

There is no definitive evidence that the concomitant administration of histamine H<sub>2</sub>-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of Advil® Cold & Flu and Advil® Pain & Head Cold Night therapy when and if these adverse reactions appear.

### **Genitourinary**

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with Advil® Cold & Flu and Advil® Pain & Head Cold Night must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out [135].

Diphenhydramine may increase urinary frequency, difficulty in urination, urinary retention and early menses [16].

Diphenhydramine is not recommended to those with bladder neck obstruction [17].

### **Hematologic** [135]

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action such as those on anti-coagulants or suffering from 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 Drug Interactions)

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anaemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Diphenhydramine has been implicated with hemolytic anemia, thrombocytopenia, agranulocytosis [16].

### **Hepatic/Biliary/Pancreatic** [135]

As with other NSAIDs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may

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

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 [73]. 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**

Ibuprofen: 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*) [136].

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 [135].

Diphenhydramine: Hypersensitivity, rash, and anaphylaxis have occurred with diphenhydramine therapy [17].

### **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 [135].



Diphenhydramine delivers a sedative effect. Alcohol and other CNS depressants may increase this effect. Caution should be used when driving a motor vehicle or operating machinery (*See Drug Interactions*) [126].

Insomnia may be a symptom of serious illness. If it persists for more than 2 weeks the patient should be re-evaluated [130].

### **Ophthalmologic**

Blurred and/or diminished vision has been reported with the use of ibuprofen and other NSAIDs, and diphenhydramine [16]. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time. Patients with glaucoma should not use Advil® Cold & Flu or Advil® Pain & Head Cold Night caplets [135].

### **Peri-Operative Considerations**

In general, NSAIDs are discontinued prior to surgeries to decrease the risk of post-operative bleeding [112].

### **Psychiatric**

See *Warnings and Precautions, Neurologic*.

For diphenhydramine, psychosis with hallucinations have been reported. Visual and auditory hallucinations, unintelligible speech and agitation have occurred[17].

### **Renal** [135]

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 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 prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a NSAID 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. Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min) ) are at risk. Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs. In these cases, utilisation of lower doses of Advil® Cold & Flu or Advil® Pain & Head Cold Night caplets should be considered and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically [135].

### **Respiratory**

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

With diphenhydramine therapy, thickening of bronchial secretions, tightening of chest, wheezing and nasal stuffiness have been reported [17].

### **Sensitivity/Resistance**

Patients sensitive to any one of the NSAIDs may be sensitive to any of the other NSAIDs also [135].

### **Sexual Function/Reproduction**

Not applicable.

### **Skin**

In rare cases, serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme) have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue. NSAIDs should be discontinued at the first appearance of rash or any other sign of hypersensitivity [137]. Diphenhydramine may trigger photosensitivity, excessive perspiration [16]. (Also see *Adverse Reactions, Dermatologic*).

### **Special Populations**

#### **Pregnant Women:**

**ADVIL® is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see Toxicology).**

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

Ibuprofen: Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. Because of the known effects of NSAIDs on the fetal cardiovascular system, use of ibuprofen during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy [135] (Also see

*Contraindications).*

Diphenhydramine: No controlled studies have been done in women or animals. Diphenhydramine may cause an increased level of uterine activity and may lead to premature labour. Caution should be exercised with its use during the latter part of pregnancy [17].

**Nursing Women:** Ibuprofen: The high protein binding and lower pH of breast milk versus plasma tend to inhibit the excretion of ibuprofen into breast milk [8]. One study showed an ibuprofen concentration of 13 ng/mL 30 minutes after ingesting 400 mg [18]. The milk:plasma ratio was 1:126. This translates to an infant exposure of 0.0008% of the maternal dose. It is not known to what extent, if any, ibuprofen crosses the human placenta [136].

Diphenhydramine: Evidence suggests that diphenhydramine may alter milk production or composition. If an alternative drug is not prescribed, infants' adequate intake of milk should be monitored. It is not known whether diphenhydramine is excreted into milk [17]. Because of the generally higher risk of antihistamines for infants and for newborns and premature babies, Advil® Cold & Flu and Advil® Pain & Head Cold Night are contraindicated in nursing mothers.

**Geriatrics (> 65 years of age):** Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from 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 [135].

The elderly are also more susceptible to the side effects of diphenhydramine: dizziness, sedation, disturbed co-ordination, and hypotension [17].

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 [135].

### **Monitoring and Laboratory Tests**

For *Warnings and Precautions* related to the use of Advil® Cold & Flu and Advil® Pain & Head Cold Night caplets and Monitoring and Laboratory Tests see *Fluid and Electrolyte Balance, Gastrointestinal, Hematologic, Hepatic, Renal and Subpopulations: Elderly*.

## ADVERSE REACTIONS

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates [138].*

### **Studies of Ibuprofen and Diphenhydramine in Combination**

In a 10-day maximum use safety and efficacy study (AE-97-08), a total of 1016 patients between 12 to >65 years of age took either one Advil PM liquid-Gel (ibuprofen 200 mg/diphenhydramine HCl 25 mg) (n= 158), or two Advil PM Liquid-Gels (ibuprofen 400 mg/diphenhydramine HCl 50 mg) (n=323), or two Tylenol PM caplets (acetaminophen 1000 mg/diphenhydramine HCl 50 mg) (n=326) or and placebo (N=167) for 10 consecutive evenings. They were instructed to begin taking the study drug on the first evening they experienced sleeplessness associated with a headache or minor aches or pains. They continued to take study medication for the next 9 consecutive evenings, regardless of whether or not they were experiencing symptoms. Although the duration of use was beyond the maximum over-the-counter duration of use (10 days versus 5 days) of ibuprofen, the daily dose was below the maximum daily dose for ibuprofen of 1200 mg and for diphenhydramine of 150 mg. The study suggests that there are no clinically relevant safety concerns associated with ibuprofen/diphenhydramine combination when administered once a day at a dose of ibuprofen / diphenhydramine hydrochloride (400 mg/50 mg or 200 mg/25 mg). [132].

In this study, although there was an increased incidence of overall nervous system adverse events and somnolence with both doses of Ibuprofen/Diphenhydramine combination compared with placebo, these rates were comparable to those observed with Tylenol PM, a currently U.S. marketed analgesic/sleep-aid product consisting of acetaminophen 1000 mg/diphenhydramine hydrochloride 50 mg. The incidences of these symptoms were similar for both doses of ibuprofen / diphenhydramine (400 mg/50 mg vs. 200 mg/25 mg). The AEs with incidence rates exceeding 2% in any treatment group are presented in Table 1. These findings were consistent within all age and gender subgroups, indicating that the use of the combination of ibuprofen and diphenhydramine by the elderly poses no additional safety concerns [132].

**Table 1. AE-97-08: Adverse Events with Incidence Rates Exceeding 2% in Any Treatment Group**

Body System	Number (%) of Subjects with AE Indicated				p-value**
	Placebo (n = 167)	1 Advil PM Liqui-Gel (n = 158)	2 Advil PM Liqui-Gels (n = 323)	2 Tylenol PM Caplets* (n = 326)	
<b>Nervous</b>	6 (3.6)	20 (12.7)	40 (12.4)	41 (12.6)	<b>0.004</b>
Somnolence	4 (2.4)	14 (8.9)	28 (8.7)	25 (7.7)	<b>0.032</b>
Dizziness	2 (1.2)	1 (0.6)	5 (1.5)	9 (2.8)	0.414
<b>Digestive</b>	21 (12.6)	16 (10.1)	39 (12.1)	50 (15.3)	0.411
Dyspepsia	15 (9.0)	11 (7.0)	16 (5.0)	25 (7.7)	0.315
Dry Mouth	1 (0.6)	1 (0.6)	7 (2.2)	5 (1.5)	0.514
<b>Body as a Whole</b>	30 (18.0)	25 (15.8)	57 (17.6)	50 (15.3)	0.818
Headache	17 (10.2)	12 (7.6)	37 (11.5)	28 (8.6)	0.500
Pain	4 (2.4)	2 (1.3)	10 (3.1)	17 (5.2)	0.134
Back Pain	8 (4.8)	5 (3.2)	8 (2.5)	5 (1.5)	0.185
<b>Respiratory</b>	7 (4.2)	9 (5.7)	9 (2.8)	10 (3.1)	0.377
Rhinitis	5 (3.0)	5 (3.2)	7 (2.2)	7 (2.1)	0.815

\* Product available in U.S. but not in Canada.

\*\*Fisher's exact test; P-values ≤ 0.05 are bolded. Note: Advil PM Liqui-Gels contain Ibuprofen 200 mg and Diphenhydramine hydrochloride 25 mg.

Two placebo-controlled, double-blind clinical trials (AE-98-01 and AE-98-02) studied subjects 16-45 years of age who had undergone surgical removal of 1 or 2 impacted third molars, one of which was at least a partial bony mandibular impaction, were given a single dose of either placebo ibuprofen (400mg) /diphenhydramine (50 mg) or 400 mg ibuprofen (n=118), before bedtime on the day of surgery.

Study AE-98-01 involved 281 subjects, with 40 receiving placebo, 122 receiving ibuprofen (400 mg) /diphenhydramine (50 mg) and 118 receiving 400 mg ibuprofen.

The active treatments were well tolerated [123]. A total of 29 adverse experiences (AEs) were reported by 25 (8.9%) subjects: 15.0% in the placebo group, 9.8% in the ibuprofen/diphenhydramine group, and 5.9% in the ibuprofen group. The AEs with incidence rates exceeding 2% in any treatment group are presented in Table 2. The incidence rates were comparable among the three treatment groups with respect to all adverse experiences, except for headache (placebo=10.0%; ibuprofen/diphenhydramine=0.8%; ibuprofen=0.8%). There were no serious AEs.

**Table 2. AE-98-01: Adverse Events with Incidence Rates Exceeding 2% in Any Treatment Group**

<b>Body System</b> Adverse Event	Placebo (n = 40)	IBU400/DPH50 (n = 122)	IBU400 (n = 119)	p-value <sup>+</sup>
<b>Any Body System</b>				
Any	6 (15.0%)	12 (9.8%)	7 (5.9%)	0.175
<b>Body as a Whole</b>				
Any	4 (10.0%)	2 (1.6%)	1 (0.8%)	0.017*
Headache	4 (10.0%)	1 (0.8%)	1 (0.8%)	0.004*
<b>Digestive</b>				
Any	1 (2.5%)	6 (4.9%)	5 (4.2%)	1.000
Nausea	0 (0.0%)	5 (4.1%)	4 (3.4%)	0.587
Vomiting	0 (0.0%)	0 (0.0%)	3 (2.5%)	0.129
Abdominal Pain	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.142
<b>Nervous</b>				
Any	1 (2.5%)	5 (4.1%)	0 (0.0%)	0.069 <sup>b</sup>
Dizziness	1 (2.5%)	4 (3.3%)	0 (0.0%)	0.129

<sup>+</sup>: Fisher's Exact test; \*: Statistically significant at  $p \leq 0.05$ ; b: Marginally significant ( $0.05 < p \leq 0.10$ ).

Study AE-98-02 involved 283 subjects, with 40 receiving placebo, 120 receiving ibuprofen (400 mg) /diphenhydramine (50 mg) and 123 receiving 400 mg ibuprofen. A total of 41 AEs were reported by 29 (10.2%) of subjects: 20.0% in the placebo group, 11.7% in the ibuprofen/diphenhydramine group, and 5.7% in the ibuprofen group [124]. The AEs with incidence rates exceeding 2% in any treatment group are presented in Table 3. There was a significant difference among the three treatment groups with respect to overall adverse experiences. There was a significant difference among the groups for digestive system AEs, and for the specific event of vomiting (placebo 5.0%; ibuprofen/diphenhydramine 0.8%; ibuprofen 0.0%). The treatment groups were comparable for other AEs and body systems. There were no serious AEs.

**Table 3. AE-98-02: Adverse Events with Incidence Rates Exceeding 2% In Any Treatment Group**

Body System Adverse Event	Placebo (n=40)	IBU400/DPH50 (n=120)	IBU400 (n=123)	p-value <sup>+</sup>
<b>Any Body System</b>				
Any	8 (20.0%)	14 (11.7%)	7 (5.7%)	0.027*
<b>Body as a Whole</b>				
Any	2 (5.0%)	9 (7.5%)	5 (4.1%)	0.461
Headache	2 (5.0%)	9 (7.5%)	5 (4.1%)	0.461
<b>Digestive</b>				
Any	6 (15.0%)	5 (4.2%)	5 (4.1%)	0.038*
Nausea	5 (12.5%)	5 (4.2%)	5 (4.1%)	0.111
Vomiting	2 (5.0%)	1 (0.8%)	0 (0.0%)	0.028*
<b>Nervous</b>				
Any	1 (2.5%)	2 (1.7%)	1 (0.8%)	0.519
Agitation	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.141
<b>Skin and Appendages</b>				
Any	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.141
Sweating	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.141

<sup>+</sup>: Fisher's Exact test

\*: Statistically significant at  $p \leq 0.05$

### **Safety Studies of Ibuprofen**

One researcher conducted an extensive analysis of published data concerning the relative safety of non-prescription doses of ibuprofen and acetaminophen [87]. 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" [87].

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 [88]. The frequency of GI AEs was similar in the placebo and ibuprofen groups (16% with placebo vs. 19% with ibuprofen). The most frequent GI AEs (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 GI AEs. Seventeen subjects (1.4%) had positive occult blood tests: the frequency was comparable for the two treatments.

In two multitransanalyses [89,90], a meta analysis [91], and a literature review [87], ibuprofen had a low incidence of GI drug reactions, comparable with that of acetaminophen and placebo.

A large-scale randomized trial comparing non-prescription 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% [97]. Ibuprofen was not statistically different from acetaminophen. Total GI 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].”

In epidemiological studies, ibuprofen has consistently exhibited the lowest relative risk of severe gastrointestinal complications compared with other NSAIDs and aspirin [92,93,94]. 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 [73]. The incidence of acute liver injury among ibuprofen users was 1.6/100,000. This was the lowest incidence among the eight NSAIDs studied and was significantly lower than the incidence among users of ketoprofen, piroxicam, fenbufen, or sulindac. For NSAID users as a group, the only factors that had an independent effect on the occurrence of acute liver injury were simultaneous use of hepatotoxic medication and the presence of rheumatoid arthritis (See *Warnings and Precautions, Hepatic/Biliary/Pancreatic*).

### **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 [136].

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 GI tract (bloating or flatulence). Incidence <1%: gastric or duodenal ulcer with bleeding and/or perforation, GI haemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase) [135].

#### **Allergic**

Incidence <1%: anaphylaxis (See *Contraindications*). Causal relationship unknown: fever, serum sickness, lupus erythematosus [135].



### **Central Nervous System**

Incidence 3–9%: dizziness. Incidence 1–3%: headache, nervousness. Incidence <1%: depression, insomnia. Causal relationship unknown: paraesthesias, hallucinations, abnormal dreams [135].

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 [135].

### **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 [135].

### **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) [135].

### **Special Senses**

Incidence 1–3%: tinnitus. Incidence <1%: amblyopia (blurred and/or diminished vision, scotomata, and/or changes in colour vision). Causal relationship unknown: conjunctivitis, diplopia, optic neuritis [135].

### **Haematologic**

Incidence <1%: leukopenia, decreases in haemoglobin and haematocrit. Causal relationship unknown: haemolytic anaemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g., purpura, epistaxis, haematuria, menorrhagia) [135].

### **Hepatic**

Liver enzyme elevations may occur in up to 15% of patients treated with ibuprofen [135].

### **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 [135].

### **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 [135].

### **Metabolic**

Incidence 1–3%: decreased appetite, oedema, fluid retention [135].

## DRUG INTERACTIONS

### Serious Drug Interactions

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

### Overview

Advil® Cold & Flu and Advil® Pain & Head Cold Night caplets are not recommended for concomitant use with any other NSAIDs, including ASA and Naproxen. Documented or possible drug interactions with Advil® Cold & Flu or Advil® Pain & Head Cold Night caplets include acetaminophen, naproxen, alcohol and other CNS depressant drugs, antihypertensives, anticoagulants, digoxin, diuretics, lithium, methotrexate, oral antidiabetic agents and insulin, 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) [138].

#### **Acetaminophen**

Although interactions have not been reported, concurrent use with Advil® Cold & Flu or Advil® Pain & Head Cold Night is not advisable: it may increase the risk of adverse renal effect [135].

#### **Acetylsalicylic acid (ASA) or other NSAIDs**

The use of Advil® Cold & Flu or Advil® Pain & Head Cold Night in addition to any other NSAID, including ASA and naproxen, is not recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for 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 [135, 136] (Also see *Contraindications*).

No clinically meaningful loss of cardioprotection was observed, when patients on low dose ASA (81 mg) were administered 400 mg ibuprofen T.I.D.[147], keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

### **Acetylsalicylic acid (ASA) Low Dose**

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

### **Alcohol and Other CNS Depressant Drugs**

Because of the possibility of additive CNS depressant effects, patients should avoid alcoholic beverages when taking Advil® Cold & Flu or Advil® Pain & Head Cold Night. (See *Warnings and Precautions, Neurologic*) [126,128]. Antidepressants such as amitriptyline, amoxapine, belladonna alkaloids, clomipramine, procarbozine and trifluromazine may increase the possibility of dry mouth, urinary retention, adynamic ileus, chronic glaucoma and altered mental status [17].

Caution is necessary if Advil® Cold & Flu or Advil® Pain & Head Cold Night are taken with other antihistamines, tranquilizers or any other sedating drug (encompassing any other diphenhydramine product including topical applications) or with prescription drugs used to treat depression [16,126,128].

### **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 [84].

### **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 [77,78] 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 [79] showed that ibuprofen 1600 mg/day for 14 days did not attenuate the antihypertensive effect of two  $\beta$ -adrenergic blockers. Houston et al [80] 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 [81]. 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 foscipril who received ibuprofen 2400 mg/day for one month [82]. In contrast, Minuz [83] 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** [135].

#### **Apomorphine** [134]

Diphenhydramine may decrease the emetic response of apomorphine in the treatment of poisoning.

#### **Coumarin-type** [75,76]

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 & Flu or Advil® Pain & Head Cold Night to patients on anticoagulants.

#### **Digoxin** [74]

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 [135].

#### **H-2 antagonists**

In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations [95,96].

**Hypoglycaemic Agents**

Ibuprofen may increase hypoglycaemic effects of oral antidiabetic agents and insulin [135].

**Lithium** [86]

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 [85]**

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**

Monoamine oxidase inhibitors, including furazolidone and procarbazine, may prolong and intensify the anticholinergic and CNS depressant effects of diphenhydramine [134].

Diphenhydramine should not be given to patients taking Eldepryl®, Marplan®, Nardil® or Parnate® [17].

**Naproxen**

Although interactions have not been reported, concurrent use with Advil Cold & Flu or Advil® Pain & Head Cold Night is not advisable: it may increase the risk.

**Selective Serotonin Reuptake Inhibitors (SSRIs) [148, 149]**

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

**Other Drugs**

Although ibuprofen binds extensively to plasma proteins, interactions with other protein-bound drugs occur rarely. Nevertheless, caution should be observed when other drugs, also having a high affinity for protein binding sites, are used concurrently. No interactions have been reported when ibuprofen has been used in conjunction with probenecid, thyroxine; antibiotics (e.g. cyclosporine), phenytoin, corticosteroids or benzodiazepines [135].

**Drug-Food Interactions**

Interactions with food have not been established.

**Drug-Herb Interactions**

Interactions with herbs have not been established.

**Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

**DOSAGE AND ADMINISTRATION****Dosing Considerations**

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

The safety issues to consider when developing a dosage regimen of Advil® Cold & Flu or Advil® Pain & Head Cold Night for individual patients are applicable to:

- Advil Cold & Flu and Advil® Pain & Head Cold Night are not recommended for elderly patients older than 65 years who are frail or debilitated. (See *Warnings and Precautions, Special Populations, Geriatrics*).

### **Recommended Dose and Dosage Adjustment**

Adults ≥16 to 65 years of age: Take 1 or 2 caplets every 6 hours to a maximum of 6 caplets per day.

### **Missed Dose**

Continue to take 1 or 2 caplets, every 6 hours as needed after a missed dose. Do not take twice the recommended dose following a missed dose [136].

### **Administration**

See *Recommended Dose and Dosage Adjustment*.

## **OVERDOSAGE**

### **Symptoms of Overdosage** [135]

Advil® Cold & Flu and Advil® Pain & Head Cold Night contain ibuprofen and diphenhydramine. The toxicity of 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 overdose. The most frequently reported symptoms of ibuprofen overdose include abdominal pain, nausea, vomiting, lethargy and drowsiness. Other CNS symptoms include headache, tinnitus, CNS depression and seizures. Metabolic acidosis, coma, acute renal failure and apnoea (primarily in very young pediatric patients) may rarely occur. Cardiovascular toxicity, including hypotension, bradycardia, tachycardia and atrial fibrillation, also has been reported [102-104].

Signs and symptoms of diphenhydramine overdose are anticholinergic in nature and can include dry mucous membranes, decreased bowel sounds, mydriasis, flushed skin, hyperthermia, drowsiness, tachycardia, urinary retention, coma, hallucinations and seizures. Death has resulted from seizures and/or cardiac arrhythmias. Cardiac arrhythmias are similar to those following an overdose of other drugs and class Ia antiarrhythmic properties and result from the blockade of fast sodium channels [129,131].

### **Treatment of Overdosage** [135]

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 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 the 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 [112]. Inducing diuresis may be helpful. The treatment of acute overdose is primarily supportive. Management of hypotension, acidosis and GI bleeding may be necessary.

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

### **Examples of Ibuprofen Overdose**

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

With electrolyte replacement and other intensive measures, a 21-month-old child recovered within 5 days after accidental ingestion of 8 g of ibuprofen [2]. A 2-year-old child who ingested approximately 8 g of ibuprofen was treated with activated charcoal, developed metabolic acidosis and acute renal insufficiency, and recovered within 72 hours [3]. A 6-year-old child became comatose after ingesting 6 g of ibuprofen [4]. He was treated with gastric lavage, charcoal, and various supportive measures and recovered within 24 hours.

### **Examples of Diphenhydramine Overdose**

In adults, ingestion of 25 mg/kg diphenhydramine hydrochloride was fatal [129].

The maximum tolerated dose of 16 grams (approximately 177 mg/kg) was reported in 1999 for a 35 year-old woman. The woman was treated with charcoal hemoperfusion and hemodialysis and recovered [139].

In patients six years of age and older, doses as low as 300 mg diphenhydramine have caused moderate toxicity (hallucinations) while doses of 1000 mg or more have been documented to cause severe toxicity (delirium/psychosis, seizures, coma) or death. Rhabdomyolysis has occurred in the absence of severe toxicity [131].

In one case report, a dose of 25 mg in a 26-year-old man resulted in agitation, confusion and paranoia; the reaction recurred when 50 mg was taken the following night. He had no underlying medical or psychiatric conditions; the only other medication taken was acetaminophen [131].

Overdose of diphenhydramine during pregnancy has been reported to produce “oxytocin like” effects of uterine sensitivity (transient, strong, regular contractions of the uterus) treatable with intravenous magnesium [140].

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

#### **Ibuprofen**

Like other nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen is an analgesic, antipyretic,



and anti-inflammatory medication [1]. The principal mechanism of action of ibuprofen and other NSAIDs is inhibition of prostaglandin biosynthesis [2].

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 [3]. Other pharmacologic effects such as lysosome and plasma membrane stabilisation have been observed, but the potential relevance of these effects to ibuprofen-induced analgesia and antipyresis is unclear.

### **Diphenhydramine**

Diphenhydramine is a first generation H<sub>1</sub> receptor antagonist of the ethanolamine class that is available over-the counter for use as a sedative, hypnotic, antihistamine, antitussive, and antiemetic agent [17].

Most antihistamines cross the blood-brain barrier and produce sedation due to inhibition of histamine *N*-methyltransferase and blockage of central histaminergic receptors. Antagonism of other central nervous system receptor sites, such as those for serotonin, acetylcholine, and alpha-adrenergic stimulation, may also be involved [127].

### **Pharmacokinetics**

#### **Absorption:**

#### **Ibuprofen**

Ibuprofen is a racemic mixture of R-(-) ibuprofen and S-(+) ibuprofen. R-(-) ibuprofen undergoes extensive (53% to 65%) enantiomeric conversion to S-(+) ibuprofen in humans, averaging between 53-65%.[9] S-(+) ibuprofen is the pharmacologically active enantiomer.

Ibuprofen is rapidly absorbed after oral administration. Serum concentrations reach a peak within 1 to 2 hours in adults [4] and in children [5,6,7]. Food decreases the rate but not the extent of ibuprofen absorption [4].

#### **Diphenhydramine**

Diphenhydramine is well-absorbed following oral administration, but undergoes first-pass metabolism in the liver and only about 40-60% of an oral dose reaches systemic circulation as unchanged diphenhydramine [16].

Following oral administration of a single dose of diphenhydramine, the drug appears in plasma within 15 minutes and peak plasma concentrations are attained within 1-4 hours [16].

Following oral administration of diphenhydramine hydrochloride dosages of 25 mg every 4 hours

or 50 mg every 6 hours, peak steady-state plasma concentrations of the drug were 55 or 85 ng/mL, respectively, and minimum peak steady-state plasma concentrations were 27.5 or 30 ng/mL, respectively [16].

**Distribution:**

**Ibuprofen**

After oral administration, the volume of distribution of ibuprofen was 0.1–0.2 L/kg in adults [8]. At therapeutic concentrations, ibuprofen is extensively bound to whole human plasma and binds primarily to site II of purified albumin [8].

**Diphenhydramine**

The distribution of diphenhydramine into human body tissues and fluid has not been fully characterized. Following IV administration in rats, highest concentrations of the drug are attained in the lungs, spleen, and brain, with lower concentrations in the heart, muscle, and liver. Following IV administration in healthy adults, diphenhydramine reportedly has an apparent volume of distribution of 188-366L [16]. The volume of distribution of the drug reportedly is larger in Asian (about 480 L) than in Caucasian adults [16,17]. The drug crosses the placenta and has been detected in milk, although the extent of distribution in milk has not been quantified [16].

Diphenhydramine is approximately 80-85% bound to plasma proteins in vitro. Less extensive protein binding of the drug has been reported in healthy Asian adults and in adults with liver cirrhosis [16].

**Metabolism:**

**Ibuprofen**

The plasma half-life ( $t_{1/2}$ ) of ibuprofen in adults and children is 1.5–2.0 hours [6,10,14]. There is no appreciable plasma accumulation of ibuprofen or its metabolites with repeated doses [4]. Two major metabolites, 2-[4-(2-carboxypropyl)phenyl] propionic acid and 2-[4-(2-hydroxy-2-methylpropyl)propionic acid, have been identified in plasma and in urine [10]. The metabolites 1-hydroxyibuprofen and 3-hydroxyibuprofen have also been found in urine in very small concentrations [11,12]. 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 [8].

Cytochrome P450 (CYP) 2C9 has been identified as the most important enzyme in the oxidative metabolism of R(-) and S(+) ibuprofen [13]. Ibuprofen does not appear to induce the formation of drug-metabolizing enzymes in rats [10].

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 [15]. Furthermore, there was no

statistically significant difference between the two age groups in the urinary excretion pattern of the drug and its major metabolites.

### **Diphenhydramine**

Diphenhydramine is rapidly and apparently almost completely metabolized. Following oral administration, the drug undergoes substantial first-pass metabolism in the liver [16,17].

Diphenhydramine appears to be metabolized principally to diphenylmethoxyacetic acid, which may further undergo conjugation. The drug also undergoes dealkylation to form *N*-demethyl and *N*, *N*-didemethyl derivatives. Diphenhydramine and its metabolites are excreted principally in the urine.

### **Excretion:**

### **Ibuprofen**

Ibuprofen is rapidly excreted in breast milk. Thirty minutes after oral ingestion of 400 mg of ibuprofen, the concentration in breast milk was found to be 13 ng/mL [18]. 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 [18]. Studies in animals indicate that ibuprofen is transported across the placenta.

### **Diphenhydramine**

Plasma concentrations of diphenhydramine appear to decline in a monophasic manner, although some pharmacokinetic data suggest a polyphasic elimination. The terminal half-life of diphenhydramine has not been fully elucidated, but appears to range from 2.4-9.3 hours in healthy adults. The terminal elimination half-life reportedly is prolonged in adults with liver cirrhosis [16].

Following oral administration of a single 100 mg dose of diphenhydramine in healthy adults, about 50-75% of the dose is excreted in the urine in 4 days, almost completely as metabolites and with most urinary excretion occurring within the first 4-48 hours. Only about 1% of a single oral dose is excreted unchanged in the urine [16].

The total body clearance of diphenhydramine decreases with age. For example, after a single 1.25 mg/kg oral (syrup) dose, the total body clearance for the elderly and children were  $11.7 \pm 3.1$  mL/min/kg versus  $49.2 \pm 22.8$  mL/min/kg, respectively [17].

The elimination half-life of diphenhydramine is prolonged with age. After a single dose administration of diphenhydramine syrup 1.25 mg/kg, elderly patients exhibited a mean half-life of 13.5 hours compared with 9.2 hours in young adults and 5.4 hours in children [17].

## **STORAGE AND STABILITY**

Advil® Cold & Flu and Advil® Pain & Head Cold Night caplets should be stored in tightly closed containers at room temperature (15-30°C).

**Other:** Keep in a safe place out of the reach of children.

## **SPECIAL HANDLING INSTRUCTIONS**

Not applicable.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Each Advil® Cold & Flu and Advil® Pain & Head Cold Night caplet contains 200 mg ibuprofen and 38 mg diphenhydramine citrate.

Non-medicinal ingredients: calcium stearate, carnauba wax, colloidal silicon dioxide, corn starch, croscarmellose sodium, FD&C blue #2, glyceryl behenate, hypromellose, lactose monohydrate, microcrystalline cellulose, polydextrose, pregelatinized starch, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, stearic acid, titanium dioxide.

The caplets are available in bottles of 20, 40.

## PART II: SCIENTIFIC INFORMATION

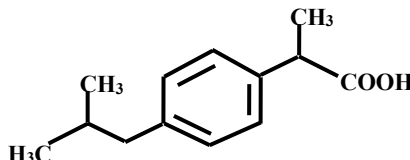
### PHARMACEUTICAL INFORMATION

#### Drug Substance

#### Ibuprofen [135]

Proper name:	Ibuprofen
Chemical name:	$\alpha$ -methyl-4-(2-methylpropyl) benzenecetic acid
Other names:	p-isobutyhydratropic acid 2-(4-isobutylphenyl)-propionic acid
Molecular formula and molecular mass:	$C_{13}H_{18}O_2$ 206.28 daltons

Structural formula:



Physical characteristics:	White or almost white powder or crystals with a characteristic odour.
Solubility:	Low solubility in water (<0.1 mg/mL), soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether, and 1 in 1.5 of acetone. Ibuprofen is also soluble in an aqueous solution of alkali hydroxides and carbonates.
pKa value:	pKa = 4.43
Melting Point:	75–78°C

## Diphenhydramine Citrate

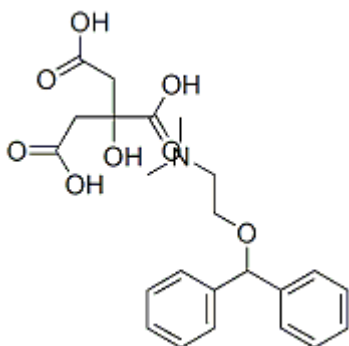
Proper name: Diphenhydramine citrate

Chemical name: 2-(diphenylmethoxy)-N,N-dimethylethanamine monocation

Molecular Formula:  $C_{17}H_{21}NO \cdot C_6H_8O_7$

Molecular Weight: 447.49

Structural Formula:



Physical characteristics: White, crystalline powder.

Solubility in Water: 0.5%

Melting Point: 146-150°C, within 2°C range

## CLINICAL TRIALS

### Study results

#### **Studies with Ibuprofen**

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 [19], headache [20-22], dental pain [23-30], muscle aches [31], and dysmenorrhea [32-37] in adults. The antipyretic efficacy of ibuprofen has been demonstrated at doses of 200 and 400 mg in adults [28,38-40].

#### **Studies with Diphenhydramine Hydrochloride**

The antihistaminic activity of diphenhydramine has been assessed by measuring the suppression of wheal and flare reaction following histamine skin testing [142-144]. Plasma diphenhydramine levels above 20 ng/mL have been found to be associated with suppression of wheal and flare formation following a single 50 mg oral dose; antagonism of wheal formation stopped when plasma diphenhydramine levels fell below 20 ng/mL [144]. Following oral and intravenous administration of 50 mg diphenhydramine levels of 25-50 ng/mL; within this plasma concentration range, diphenhydramine exhibited significant antihistaminic activity without significant sedation [142]. A single oral dose of diphenhydramine 1.25 mg/kg administered to elderly adults, young adults, and children (mean dose 86, 88 and 40 mg/kg, respectively) produced more pronounced antihistaminic response in children than in the young and elderly adults with E<sub>max</sub> values (the maximum effect attributable to the drug) [145] of 99.8%, 45.7% and 35.3 %, respectively [143]. EC<sub>50</sub> values ( the drug concentration producing 50% of the E<sub>max</sub>) were 7.8, 8.0, 38.7 ng/mL, for the elderly adults, young adults, and children, respectively [143]

#### **Studies with Ibuprofen and Diphenhydramine Citrate**

A preliminary pharmacokinetic study assessed the pharmacokinetics of ibuprofen 2 x 200 mg clinical capsules and diphenhydramine citrate 2 x 38 mg capsules administered simultaneously compared to that of each drug administered individually under fasted conditions [133]. This study showed that there were no interactions between ibuprofen and diphenhydramine when the two drugs were administered simultaneously under fasted conditions. As shown in tables 3 and 4, the pharmacokinetic profiles of both drugs were similar whether administered in combination or individually.

**Table 3. WM-716: Diphenhydramine pharmacokinetic Parameters: Mean ± Standard Deviation [133]**

Treatment (sample size)	C <sub>max</sub>	AUCI ng-hr/mL	T <sub>max</sub> (hr)	t ½	Kel (1/hr)
DPH citrate 76 mg (A) (n=23)	56.3 ± 15.9	598.8 ± 199.0	2.95 ± 1.00	9.64 ± 2.08	0.08 ± 0.02
DPH citrate 76 mg + IBU 400 mg (C) (n=23)	61.7 ± 23.9	608.7 ± 211.9	2.76 ± 0.69	10.10 ± 2.36	0.07 ± 0.02
C/A Ratio <sup>+</sup>	107.4%	101.4%	--	--	--
C/A 90% CI <sup>+</sup>	99.7-115.7%	95.9-107.3%	--	--	--

DPH = Diphenhydramine

IBU= Ibuprofen

<sup>+</sup>derived from log-transferred data.

--=Not done.

**Table 4. WM-716: Ibuprofen pharmacokinetic Parameters: Mean ± Standard Deviation [133]**

Treatment (sample size)	C <sub>max</sub>	AUCI ng-hr/mL	T <sub>max</sub> (hr)	t ½	Kel (1/hr)
IBU 400 mg (B) (n=23)	36.1 ± 7.4	112.7 ± 24.9	1.42 ± 1.13	1.83 ± 0.30	0.39 ± 0.06
DPH citrate 76 mg + IBU 400 mg (C) (n=23)	36.4 ± 7.0	109.5 ± 27.6	1.35 ± 0.99	1.82 ± 0.29	0.39 ± 0.06
C/B Ratio <sup>+</sup>	101.2%	96.5%	--	--	--
C/B 90% CI <sup>+</sup>	94.8-108.2%	92.6-100.6%	--	--	--

DPH = Diphenhydramine

IBU= Ibuprofen

<sup>+</sup>derived from log-transferred data.

--=Not done.

**Comparative Bioavailability Study ( Volume 4, Section 11.4.1.3 and Volume 2 Section 2.5)**

A single-dose, randomized, 3-way crossover, comparative bioavailability study was performed on healthy volunteers under fasting conditions. The rate and extent of absorption of ibuprofen and diphenhydramine was measured and compared following a 2-unit single oral dose of Advil® Cold & Flu/Advil® Pain & Head Cold Night (Ibuprofen 200 mg and Diphenhydramine citrate 38 mg), Advil Caplets (Ibuprofen 200 mg) (a Wyeth Consumer Healthcare Inc. product) and Dimetane Allergy Tablets (Diphenhydramine citrate 38 mg) ( a Wyeth Consumer Healthcare Inc. product). The results from measured data from 28 subjects (15 males and 13 females) are summarized in Table 5 and 6.



**Summary Tables of the Comparative Data**  
**Table 5**

Ibuprofen ( 2 x 200 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test* (n=28)	Reference† (n=28)	% Ratio of Geometric Means	Confidence Interval (90%)
AUC <sub>T</sub> (µg·hr/mL)	147.77 151.32 (23.56)	149.88 153.07 (21.09)	98.59%	95.97% to 101.28%
AUC <sub>I</sub> (µg·hr/mL)	152.64 156.48 (23.84)	155.49 159.41 (23.43)	98.19%	95.69% to 100.75%
C <sub>max</sub> (µg/mL)	37.14 37.59 (15.11)	37.54 37.92 (14.17)	99.01%	94.68% to 103.52%
T <sub>max</sub> § (h)	1.50 (0.50 - 5.00)	1.75 (0.50 - 4.00)		
T <sub>½</sub> ε (h)	2.21 (17.97)	2.20 (17.32)		

\* 2 × Advil® Cold & Flu/Advil Pain® & Head Cold Night caplets (Ibuprofen 200 mg and Diphenhydramine Citrate 38 mg) (Wyeth Consumer Healthcare, Mississauga ON, Canada)

† 2 × Advil® (Ibuprofen) 200 mg Tablets/Caplets, (Wyeth Consumer Healthcare, Mississauga ON, Canada)

§ Expressed as median (range) only

ε Expressed as the arithmetic mean (CV%) only

**Table 6**

Diphenhydramine (2 x 38 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test* (n=28)	Reference† (n=27)	% Ratio of Geometric Means	Confidence Interval (90%)
AUC <sub>T</sub> (ng·hr/mL)	657.10 705.69 (38.86)	635.09 681.93 (36.98)	103.71%	98.85% to 108.82%
AUC <sub>I</sub> (ng·hr/mL)	705.41 764.61 (41.07)	684.21 741.92 (39.61)	103.29%	98.55% to 108.26%
C <sub>max</sub> (ng/mL)	81.74 87.13 (37.70)	73.17 77.83 (35.83)	112.55%	103.48% to 122.42%
T <sub>max</sub> § (h)	1.78 (0.75- 5.00)	2.25 (1.00- 5.00)		
T <sub>½</sub> ° (h)	9.40 (18.42)	9.48 (19.04)		

\* 2 × Advil® Cold & Flu/Advil Pain® & Head Cold Night caplets (Ibuprofen 200 mg and Diphenhydramine Citrate 38 mg) (Wyeth Consumer Healthcare, Mississauga ON, Canada)

† 2 × Dimetane Allergy (Diphenhydramine Citrate) 38 mg Tablets (Wyeth Consumer Healthcare, Mississauga ON, Canada)

§ Expressed as median (range) only

° Expressed as the arithmetic mean (CV%) only

**Under fasting conditions, Ibuprofen and Diphenhydramine administered as Advil® Cold & Flu/Advil Pain® and Head Cold Night caplets were found to be bioequivalent to Ibuprofen administered as Advil Caplets alone, and Diphenhydramine administered as Dimetane Allergy Tablets alone.**

## DETAILED PHARMACOLOGY

### **Ibuprofen**

#### **Animal Pharmacology**

Cyclooxygenase inhibitors such as ibuprofen and other NSAIDs reduce thromboxane A<sub>2</sub> production and release, thereby decreasing platelet aggregation [105]. Like many other NSAIDs, ibuprofen inhibits platelet aggregation, as demonstrated in vivo by prevention of platelet disposition in aortopulmonary arterial bypass grafts in dogs [106]. The drug's protective action against pulmonary embolism in rabbits injected intravenously with arachidonic acid may also

relate to inhibition of platelet aggregation [107,108]. The decreased platelet aggregation may be due in part to a reduction in membrane fluidity [109]. Ibuprofen may also reduce platelet membrane fluidity, which reduces aggregation [110], but it is not known to what extent TXA<sub>2</sub> synthesis inhibition is involved in this effect.

The penetration of ibuprofen into rabbit and rat foetuses was investigated. Rabbits and rats in late pregnancy were given single oral doses of 60 and 20 mg/kg respectively of C<sup>14</sup>-labeled ibuprofen [105]. 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**

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 as 2-(2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-(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 [105].

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 [136].

### **Diphenhydramine**

#### **Human Pharmacology**

Seven intensive care patients were studied for the effects of cimetidine, an H<sub>2</sub> antagonist on cardiovascular parameters with and without premedication. Cimetidine 200 mg was administered IV on Day 1. Mean arterial pressure dropped within 2 minutes and remained below baseline for the 8 minute measurement period. Diphenhydramine, an H<sub>1</sub> antagonist, was administered as 40 mg IV 5 minutes before administering cimetidine 200 mg IV on day 2. Mean arterial pressure did not change. The authors concluded that cimetidine has enough H<sub>1</sub>-receptor characteristics to affect blood pressure [17].

#### **MICROBIOLOGY**

Not applicable.

## TOXICOLOGY

### **Ibuprofen**

Single-dose toxicity studies have been conducted in mice, rats, and dogs [105]. The LD<sub>50</sub> values for ibuprofen in mice and rats, expressed as mg/kg of body weight, are as follows:

Mice	Oral	800 mg/kg
	Intraperitoneal	320 mg/kg
Rats	Oral	1600 mg/kg
	Subcutaneous	1300 mg/kg

Acute signs of poisoning were prostration in mice and sedation, prostration, loss of righting reflex, and laboured respiration in rats. Death occurred within 3 days from perforated gastric ulcers in mice and intestinal ulceration in rats, irrespective of the route of administration. Single ibuprofen doses of 125 mg/kg and above in dogs caused emesis, transient albuminuria, faecal blood loss, and erosions in the gastric antrum and pylorus. No ill effects were seen with doses of 20 or 50 mg/kg [105].

The primary toxic effect of ibuprofen in repeated doses in rats is intestinal damage [105]. At a dosage of 180 mg/kg/day for 26 weeks, ibuprofen alters the organ-to-body weight ratio of certain organs, such as the liver, kidneys, gonads, and secondary sex organs, although no histological abnormalities have been observed and the effects are reversible. The liver and kidney enlargement may be a reflection of work hypertrophy associated with the metabolism and excretion of the compound, whereas the significance of the effects on other organs is unknown. When administered in lethal doses (540 mg/kg/day), ibuprofen produces mild kidney lesions in addition to intestinal damage.

In rats given 180 mg/kg/day of ibuprofen orally for 55 weeks and 60 mg/kg/day for the next 60 weeks, the only specific pathological effect observed was intestinal ulceration [111]. 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 [105].

### **Diphenhydramine Citrate**

The LD<sub>50</sub> value for diphenhydramine in rats is 500 mg/kg.

No data is available on reproduction studies in animals receiving diphenhydramine citrate.

### **Ibuprofen and Diphenhydramine Hydrochloride**

#### **Acute Toxicity Studies**

The LD<sub>50</sub> values for ibuprofen, diphenhydramine and ibuprofen/diphenhydramine combination in rats, expressed as mg/kg of body weight, are as follows:

		<b>LD<sub>50</sub></b>
Ibuprofen		1225 mg/kg
Diphenhydramine		275 mg/kg
IBU/DPH Combination	2:1	700 mg/kg
	4:1	840 mg/kg
	8:1	880 mg/kg

No toxicological interactions between the two drugs were observed [113].

### **Repeat Dose Toxicity Studies**

In the 2- and 13-week repeat-dose toxicity studies rats given ibuprofen alone or in combination with diphenhydramine showed no definite difference in the findings in the drug combinations given at 4:1 or 8:1 [114,115]. In the 2-week study, the no observable effect level (NOEL) for the drug combination of ibuprofen and diphenhydramine was determined to be 24 mg/kg/day and 6 mg/kg/day, respectively [114].

In the 13-week study, rats given ibuprofen alone (16 mg/kg/day) or in combination with diphenhydramine (50:12.5 and 100:25 mg/kg/day) showed renal papillary necrosis or edema, or both. In addition, rats in these groups showed gastrointestinal (GI) toxicity characteristic of propionic acid non-steroidal anti-inflammatory drugs (NSAIDs). Secondary effects included decreased hemograms suggesting GI bleeding, which is a characteristic adverse effect from treatment with NSAIDs. There was no indication that the ibuprofen effect was potentiated by the addition of diphenhydramine. A NOEL was calculated for the drug combination of 25:6.25 mg/kg/day [115].

In dogs, the data from all parameters and examinations did not suggest that any adverse effect of the drug combination was different than those seen from the individual components [116, 117]. However, dogs were given considerably lower doses of ibuprofen and diphenhydramine, alone and in combination, compared to those used to dose rats. It is well known that dogs are more sensitive to the adverse effects of NSAIDs, especially ibuprofen, compared to rats; therefore, it was appropriate to use the lower doses in dogs. In the 2-week study, no result from any examination revealed any finding that could be attributed to ibuprofen, diphenhydramine, alone or in combination [116]. In the dog studies the maximum tolerated dose was the high dose (16:4 mg/kg/day) of the 13-week study [117].

### **Teratology Studies**

In the teratology studies in rats and rabbits at the high dose (60:15 mg/kg/day, ibuprofen:diphenhydramine) there were reduced weight gains in both species during the treatment periods, but not during the overall duration of the study [118,119,120,121,122]. None of the doses, including the high dose, caused any embryotoxic, fetotoxic, or teratogenic effects.

Overall, ibuprofen induced prototypical GI lesions characterized by erosions and ulcers. In addition, many animals at the higher doses showed renal papillary necrosis and/or edema. Rats and dogs are highly sensitive to NSAIDs compared to humans and, therefore, presented with these findings. Diphenhydramine is an antihistaminic drug with sedative properties. Animals

given the high doses of this drug showed darkening or reddening of the major organs in the thorax and abdomen. The cause of these findings may result from physiologic depression resulting in decreased blood circulation with stasis occurring in these tissues. Rats who received diphenhydramine in the acute studies usually died within the first day or so after dosing, earlier than rats given ibuprofen. There was no indication of drug: drug interaction in any of the studies with the proposed combination drug product.

### **Genotoxicity**

Ibuprofen has shown no genotoxicity in the in vitro bacterial mutation assay in the presence and absence of S9 using *Salmonella* Typhimurium TA1535, TA1538, TA97a, TA100 and TA102.[150,151] It was also tested in an in vivo sister chromatid exchange assay in the bone marrow cells of mice dosed orally or intraperitoneal and showed weak genotoxicity in the sister chromatid assay. There was no difference in the occurrence of chromosomal aberrations in cultured human lymphocytes in patients before or after treatment with ibuprofen [152]. A recent study in mouse bone marrow cells suggested a potential for chromosomal aberrations after oral dosing [153]. Overall, it was not genotoxic in vitro but was weakly mutagenic in vivo.

### **Carcinogenic Potential**

Thirty male and thirty 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. [111]

### **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 C<sup>14</sup> 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. [105]

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**PART III: CONSUMER INFORMATION****Advil® Cold & Flu  
Ibuprofen and Diphenhydramine Citrate Caplets**

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

**ABOUT THIS MEDICATION****What the medication is used for:**

Advil Cold & Flu is used for the temporary relief of the symptoms associated with colds and influenza (the "flu"):

- Body aches and pain
- Sore throat pain
- Fever
- Headache
- Runny nose
- Itchy watery eyes
- Sneezing

**What it does:**

Ibuprofen relieves pain and reduces fever. Diphenhydramine citrate, an antihistamine, relieves the cold and flu symptoms.

**When it should not be used:**

Do not use Advil Cold & Flu if you have or are:

- allergic/hypersensitive to ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA) or other salicylates, diphenhydramine or to any ingredient in the formulation or component of the container, or any of Advil Cold & Flu ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section),
- active or recurrent stomach ulcer, gastrointestinal (GI) bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis),
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms
- serious liver or kidney disease,
- high potassium in blood,
- taking any of the following medications:
  - acetaminophen
  - ASA
  - antihistamines and or diphenhydramine containing products, (e.g. for cough & cold, sleep aids, etc.)
  - monoamine oxidase inhibitors (MAOIs)
  - NSAIDs, such as naproxen and ibuprofen,
- dehydrated (significant fluid loss) due to vomiting,

- diarrhea or lack of fluid intake,
- heart problems, such as high blood pressure or severe coronary artery disease,
- right before or after heart surgery,
- System Lupus Erythematosus,
- in your third trimester of pregnancy.

**What the medicinal ingredients are:**

Ibuprofen and diphenhydramine citrate

**What the nonmedicinal ingredients are:**

calcium stearate, carnauba wax, colloidal silicon dioxide, corn starch, croscarmellose sodium, FD&C blue #2, glyceryl behenate, hypromellose, lactose monohydrate, microcrystalline cellulose, polydextrose, pregelatinized starch, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, stearic acid, titanium dioxide.

**What dosage forms it comes in:**

Each caplet contains ibuprofen 200 mg and diphenhydramine citrate 38 mg

**WARNINGS AND PRECAUTIONS** **Serious Warnings and Precautions**

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

Patients at risk of kidney problems, including the elderly or those using diuretics.

Use during pregnancy or nursing should be avoided.

Stop use immediately if you have difficulty or pain when urinating.

May cause marked drowsiness.

**BEFORE you use Advil Cold & Flu talk to your doctor or pharmacist if you have/have had or if you:**

- previous or current stomach ulcers, diabetes, thyroid disease, mild to moderate kidney disease, mild to moderate liver disease, heart disease, glaucoma, breathing problems or chronic lung disease (such as asthma, emphysema or chronic bronchitis), blood clotting disorder (such as hemophilia), difficulty in urination due to prostate enlargement or bladder neck obstruction, any other serious condition, are taking any other prescription or over-the-counter drug, including any other anti-inflammatory medication
- are trying to conceive, are in your first or second trimester of pregnancy, are breastfeeding

Use with caution in the elderly.

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

Avoid alcoholic beverages while taking this product.  
Do not drive motor vehicle or operate machinery.

Consult a doctor if pain/fever lasts more than 3 days or if flu symptoms last more than 5 days.

### INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking:

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

Drugs that may interact with Advil Cold & Flu include:

Acetaminophen, anticoagulants (blood thinners), apomorphine, alcohol, digoxin, antidiabetic agents (oral) and insulin, diuretics, methotrexate, lithium, probenecid, thyroxine, antibiotics (e.g. cyclosporine), phenytoin, corticosteroids, benzodiazepines, blood pressure medications, depression medications, monoamine oxidase inhibitors (MAOIs), antihistamines (such as allergy medications), tranquilisers or other sedating drugs, NSAIDs (including naproxen and ibuprofen), sleep-aids, cold medications

Do not use a topically-applied diphenhydramine product at the same time as Advil Cold & Flu.

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

### PROPER USE OF THIS MEDICATION

#### Usual dose:

Children and Adults 16 to 65 years: Take 1 or 2 caplets every 6 hours as needed to a maximum of 6 caplets per day. Do not exceed the single or maximum recommended daily dosage.

Do not give to children under 16 or adults over 65 years old unless directed by a physician.

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

#### Overdose

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

#### Missed Dose:

Continue to take 1 or 2 caplets every 6 hours. Do not take twice the recommended dose following a missed dose.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.

If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness, any change in vision, fluid retention, shortness of breath, wheezing, any trouble breathing or chest tightness, hives, swelling or itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, jaundice (yellowing of the eyes or skin due to liver problem) or any other side effect or unexplained symptoms develop while taking Advil Cold & Flu discontinue use immediately and contact a physician.

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

*This is not a complete list of side effects. For any unexpected effects while taking Advil Cold & Flu, contact your doctor or pharmacist.*

### REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

### HOW TO STORE IT

Store at room temperature (15°-30°C) in a tightly closed container.

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

### MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Pfizer Consumer Healthcare, a division of Pfizer Canada ULC, Mississauga, Ontario L5R 4B2, at: 1-888--869-9384

This leaflet was prepared by Pfizer Consumer Healthcare, a division of Pfizer Canada ULC

Last revised: October 16, 2019

**PART III: CONSUMER INFORMATION****Advil® Pain & Head Cold Night  
Ibuprofen and Diphenhydramine Citrate Caplets**

This leaflet is part III of a three-part "Product Monograph" published when **Advil Pain & Head Cold Night** 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 Pain & Head Cold Night**. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

Advil Pain & Head Cold Night is used for the temporary relief of the symptoms associated with colds and influenza (the "flu"):

- Body aches and pain
- Sore throat pain
- Fever
- Headache
- Runny nose
- Itchy watery eyes
- Sneezing

**What it does:**

Ibuprofen relieves pain and reduces fever. Diphenhydramine citrate, an antihistamine, relieves the cold and flu symptoms.

**When it should not be used:**

Do not use Advil Pain and Head Cold Night if you have or are:

- allergic/hypersensitive to ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA) or other salicylates, diphenhydramine or to any ingredient in the formulation or component of the container, or any of Advil Cold & Flu ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section)
- active or recurrent stomach ulcer, gastrointestinal (GI) bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis)
- nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), urticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms
- serious liver or kidney disease
- high potassium in the blood
- taking any of the following medications:
  - acetaminophen
  - ASA
  - antihistamines and or diphenhydramine containing products, (e.g. for cough & cold, sleep aids, etc.)
  - monoamine oxidase inhibitors (MAOIs)
  - NSAIDs, such as naproxen and ibuprofen
- dehydrated (significant fluid loss) due to vomiting,

- diarrhea or lack of fluid intake
- heart problems, such as high blood pressure or severe coronary artery disease
- right before or after heart surgery
- System Lupus Erythematosus
- in your third trimester of pregnancy.

**What the medicinal ingredients are:**

Ibuprofen and diphenhydramine citrate

**What the nonmedicinal ingredients are:**

calcium stearate, carnauba wax, colloidal silicon dioxide, corn starch, croscarmellose sodium, FD&C blue #2, glyceryl behenate, hypromellose, lactose monohydrate, microcrystalline cellulose, polydextrose, pregelatinized starch, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, stearic acid, titanium dioxide.

**What dosage forms it comes in:**

Each caplet contains ibuprofen 200 mg and diphenhydramine citrate 38 mg

**WARNINGS AND PRECAUTIONS****Serious Warnings and Precautions**

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

Patients at risk of kidney problems, including the elderly or those using diuretics.

Use during pregnancy or nursing should be avoided.

Stop use immediately if you have difficulty or pain when urinating.

May cause marked drowsiness.

**BEFORE** you use Advil Pain & Head Cold Night talk to your doctor or pharmacist if you have/have had or if you:

- previous or current stomach ulcers, diabetes, thyroid disease, mild to moderate kidney disease, mild to moderate liver disease, heart disease, glaucoma, breathing problems or chronic lung disease (such as asthma, emphysema or chronic bronchitis), blood clotting disorder (such as hemophilia), difficulty in urination due to prostate enlargement or bladder neck obstruction, any other serious condition, are taking any other prescription or over-the-counter drug, including any other anti-inflammatory medication
- are trying to conceive, are in your first or second trimester of pregnancy, are breastfeeding

Use with caution in the elderly.

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

Avoid alcoholic beverages while taking this product.  
Do not drive motor vehicle or operate machinery.  
Consult a doctor if pain/fever lasts more than 3 days or if flu symptoms last more than 5 days.

### INTERACTIONS WITH THIS MEDICATION

Do not use this product if you are taking:

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

Drugs that may interact with Advil® Pain & Head Cold Night include:

Acetaminophen, anticoagulants (blood thinners), apomorphine, alcohol, digoxin, antidiabetic agents (oral) and insulin, diuretics, methotrexate, lithium, probenecid, thyroxine, antibiotics (e.g. cyclosporine), phenytoin, corticosteroids, benzodiazepines, blood pressure medications, depression medications, mononamine oxidase inhibitors (MAOIs), antihistamines (such as allergy medications), tranquilisers or other sedating drugs, NSAIDs (including naproxen and ibuprofen), sleep-aids, cold medications

Do not use a topically-applied diphenhydramine product at the same time as Advil Pain & Head Cold Night.

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

### PROPER USE OF THIS MEDICATION

#### Usual dose:

Children and Adults 16 to 65 years: Take 1 or 2 caplets every 6 hours as needed to a maximum of 6 caplets per day. Do not exceed the single or maximum recommended daily dosage.

Do not give to children under 16 or adults over 65 years old unless directed by a physician.

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

#### Overdose

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

#### Missed Dose:

Continue to take 1 or 2 caplets every 6 hours. Do not take twice the recommended dose following a missed dose.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Take with food or milk if upset stomach occurs.

If abdominal pain, heartburn, nausea or vomiting, bloating, diarrhea or constipation, ringing or buzzing in the ears, nervousness, sleeplessness, dizziness, any change in vision, fluid retention, shortness of breath, wheezing, any trouble breathing or chest tightness, hives, swelling or itching, skin rashes, skin reddening, blisters, blood in vomit, bloody or black stools, jaundice (yellowing of the eyes or skin due to liver problem) or any other side effect or unexplained symptoms develop while taking Advil Pain & Head Cold Night discontinue use immediately and contact a physician.

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

*This is not a complete list of side effects. For any unexpected effects while taking Advil Pain & Head Cold Night, contact your doctor or pharmacist.*

### REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

### HOW TO STORE IT

Store at room temperature (15°-30°C) in a tightly closed container.

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

### MORE INFORMATION

This document plus the full product monograph, prepared for

health professionals can be obtained by contacting the sponsor, Pfizer Consumer Healthcare, a division of Pfizer Canada ULC, Mississauga, Ontario L5R 4B2, at: 1-888- 869-9384

This leaflet was prepared by Pfizer Consumer Healthcare, a division of Pfizer Canada ULC

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