PRODUCT MONOGRAPH

ADVIL® NIGHTTIME

Ibuprofen 200 mg and Diphenhydramine Hydrochloride 25 mg Capsules

Analgesic/Sleep Aid

GlaxoSmithKline Consumer Healthcare ULC
55 Standish Court, Suite 450
Mississauga, Ontario
L5R 4B2

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Liqui-gel: ibuprofen 200 mg (as free acid and potassium salt) diphenhydramine hydrochloride 25 mg	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Advil Nighttime (Ibuprofen and Diphenhydramine Hydrochloride Capsule) is a nonprescription analgesic and sleep aid preparation to be taken as a single dose of 1 or 2 capsules at bedtime. Advil Nighttime is indicated for:

For occasional use, for a limited period of time (five days or less) for the relief of acute nighttime pain and accompanying sleeplessness and, in these circumstances, for increased duration of sleep uninterrupted by pain.

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. The use of Advil Nighttime in this population should only be recommended after evaluation on individual basis for sleeplessness due to acute pain by a physician.

Pediatrics (<16 years of age):
Advil Nighttime is 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.

- 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.

- 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.

- Do not use Advil Nighttime during the last 3 months of pregnancy [17].

- Ibuprofen should not be used right before or after heart surgery

- 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 Nighttime is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

- 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).

- Ibuprofen should not be used during the third trimester of pregnancy because of risk of

premature closure of the ductus arteriosus, and prolonged parturition.

- Children and adolescents (see Indications)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Causes sedation or sleepiness. Not for daytime use**.**
- Caution in patients prone to gastrointestinal tract irritation (See *Warnings and Precautions, Gastrointestinal and Drug Interactions, Coumarin-type anticoagulants*).
- 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*).
- 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*).
- Risk in Pregnancy: Caution should be exercised in prescribing Advil products during the first and second trimesters of pregnancy or breastfeeding. Use of NSAIDS at approximately 20 weeks of gestation or later may cause oligohydramnios, and renal dysfunction including renal failure (See *Oligohydramnios/Neonatal Renal Impairment*, *Pregnant Women* and *Breast-feeding*).
- Ibuprofen is contraindicated for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see *CONTRAINDICATIONS*).

General

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

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 who suffer from sleeplessness without pain and pain that does not cause sleeplessness should not take this product.

Patients with glaucoma, chronic lung disease (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 acute pain and sleeplessness caused by pain do not improve within 5 days or are accompanied by fever, patients should stop use and consult a physician.

Carcinogenesis and Mutagenesis
Not applicable.

Cardiovascular
Ibuprofen: Congestive heart failure in patients with marginal cardiac function, elevated blood pressure and palpitations.

Long term continuous use may increase the risk of heart attack or stroke [136].

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.

Fluid and Electrolyte Balance
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 Nighttime 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

Serious gastrointenstinal (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 Nighttime 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 Nighttime 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 H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of Advil Nighttime 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 Nighttime must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

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

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

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*).

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.

Diphenhydramine: Hypersensitivity and analphylaxis 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.

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 Nighttime.

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 audatory hallucinations, unintelligible speech and agitation have occurred [17].

Renal
Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis 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 Nighttime should be considered and patients carefully monitored.

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

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

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

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

Sexual Function/Reproduction
Not applicable.

Skin
In rare cases, serious skin reactions (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. Diphenhydramine may trigger photosensitivity, excessive perspiration. (Also see *Adverse Reactions, Dermatologic*).

Special Populations

Pregnant Women

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

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).

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

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.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. As with other drugs

known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats.

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.

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 Nighttime is contraindicated in nursing mothers.

Oligohydramnios/Neonatal Renal Impairment: Use of NSAIDs, including Advil products, at approximately 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some more severe cases, neonatal respiratory, musculoskeletal and renal problems (see *TOXICOLOGY*).

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

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

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

effective dose and shortest duration possible.

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

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

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 acetylsalicyclic 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.

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.

Monitoring and Laboratory Tests

For Monitoring and Laboratory Tests related to the use of Advil Nighttime see *WARNINGS AND PRECAUTIONS, Fluid and Electrolyte Balance*, *Gastrointestinal*, *Hematologic*, *Hepatic*, *Renal* and *Subpopulations: Geriatrics*.

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

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.

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 Nighttime liqui-gel (ibuprofen 200 mg/diphenhydramine HCl 25 mg) (n= 158),or two Advil Nighttime liqui-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 Advil Nighttime liqui-gels 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 finding 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

	Number (%) of Subjects with AE Indicated				
Body System	**Placebo (n = 167)**	**1 Advil Nighttime Liqui-Gel (n = 158)**	**2 Advil Nighttime Liqui-Gels (n = 323)**	**2 Tylenol PM Caplets* (n = 326)**	**p-value****
Nervous	6 (3.6)	20 (12.7)	40 (12.4)	41 (12.6)	**0.004**
Somnolence	4 (2.4)	14 (8.9)	28 (8.7)	25 (7.7)	**0.032**
Dizziness	2 (1.2)	1 (0.6)	5 (1.5)	9 (2.8)	0.414
Digestive	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
Body as a Whole	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
Respiratory	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 $\leq$ 0.05 are bolded.

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

Body System Adverse Event	Placebo (n = 40)	IBU400/DPH50 (n = 122)	IBU400 (n = 119)	p-value+
Any Body System				
Any	6 (15.0%)	12 (9.8%)	7 (5.9%)	0.175
Body as a Whole				
Any	4 (10.0%)	2 (1.6%)	1 (0.8%)	0.017*
Headache	4 (10.0%)	1 (0.8%)	1 (0.8%)	0.004*
Digestive				
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
Nervous				
Any	1 (2.5%)	5 (4.1%)	0 (0.0%)	0.069b
Dizziness	1 (2.5%)	4 (3.3%)	0 (0.0%)	0.129

+: 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 41AEs 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+
Any Body System				
Any	8 (20.0%)	14 (11.7%)	7 (5.7%)	0.027*
Body as a Whole				
Any	2 (5.0%)	9 (7.5%)	5 (4.1%)	0.461
Headache	2 (5.0%)	9 (7.5%)	5 (4.1%)	0.461
Digestive				
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*
Nervous				
Any	1 (2.5%)	2 (1.7%)	1 (0.8%)	0.519
Agitation	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.141
Skin and Appendages				
Any	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.141
Sweating	1 (2.5%)	0 (0.0%)	0 (0.0%)	0.141

+: 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 recognise 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."

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 multitrial analyses [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.

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).

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

Central Nervous System
Incidence 3–9%: dizziness. Incidence 1–3%: headache, nervousness. Incidence <1%: depression, insomnia. Causal relationship unknown: paraesthesias, hallucinations, abnormal dreams.

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

Dermatologic
Incidence 3–9%: rash (including maculopapular type). Incidence 1–3%: pruritus. Incidence <1%: vesiculobullous eruptions, urticaria, erythema multiforma. Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

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

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

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

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

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

Endocrine
Causal relationship unknown: gynecomastia, hypoglycaemic reaction. Menstrual delays of up to 2 weeks and dysfunctional uterine bleeding occurred in nine patients taking ibuprofen, 400 mg t.i.d., for three days before menses.

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

DRUG INTERACTIONS

Serious Drug Interactions

- With acetaminophen may increase the risk of adverse renal effect.
- With acetylsalicylic acid (ASA), other NSAIDs including ibuprofen may result in possible additive side effects (See *Warnings and Precautions*).
- Monoamine oxidase inhibitors (MAOI's), tranquilisers, sleep-aids, other analgesics
- 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 Nighttime is not recommended for concomitant use with any other NSAIDs, including ASA and Naproxen. Documented or possible drug interactions with Advil Nighttime 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).

Acetaminophen

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

Acetylsalicylic acid (ASA) or other NSAIDs

The use of Advil Nighttime 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 (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.[137] 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 Nighttime. (See *Warnings and Precautions, Neurologic*) [126,128]. Antidepressants such as amitriptyline, amoxapine, belladonna alkaloids, clomipramine, procarbozine and triflupromazine may increase the possibility of dry mouth, urinary retention, adynamic ileus, chroninic glaucoma and altered mental status [17].

Caution is necessary if Advil Nighttime is 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 β-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 hydrochlorothioazide and fosinopril 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**.

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 Nighttime 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.

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.

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 anticholergic 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 Nighttime is not advisable: it may increase the risk.

Selective Serotonin Reuptake Inhibitors (SSRIs)[138, 139]
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, steroids, antibiotics or benzodiazepines.

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

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

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

DOSAGE AND ADMINISTRATION

Dosing Considerations
The safety issues to consider when developing a dosage regimen of Advil Nighttime for individual patients is applicable to:

- Advil Nighttime is 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 a single dose of 1 or 2 liqui-gels, at night if unable to fall asleep or go back to sleep, due to pain.

Do not exceed 1200 mg of ibuprofen (including the 200-400 mg from Advil Nighttime dose) and 300 mg diphenhydramine (including the 25-50 mg from Advil Nighttime dose, if this is being taken during the day as an antihistamine) in 24 hours. Advil Nighttime can be taken 4 hours after the last ibuprofen and/or diphenhydramine dose. Do not recommend Advil Nighttime use for more than 5 consecutive nights without evaluating the causes for sleeplessness with pain.

Missed Dose
Advil Nightime should be taken only once during the evening or night. Do not take twice the recommended dose after a missed dose.

Administration
See *Recommended Dose and Dosage Adjustment*.

OVERDOSAGE

Symptoms of Overdosage
Advil Nighttime contains ibuprofen and diphenhydramine hydrochloride. 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 overdosage. 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, have also 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, tachyardia, urinary retention, coma, hallucinations and seizures. Death has resulted from seizures and/or cardiac arythmias. Cardiac arrhythmias are similar to those following an overdose of other drugs and class Ia antiarrhytmic properties and result from the blockade of fast sodium channels [129,131].

Treatment of Overdosage

In cases of acute overdose, the stomach should be emptied through induction of emesis (in alert patients only) or gastric lavage. Due to the rapid absorption of 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.

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 Hydrochloride Overdose

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

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.

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 Hydrochloride
Diphenhydramine is a first generation H_1 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 Hydrochloride
Diphenhydramine hydrochloride 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 Hydrochloride
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 (t½) 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 Hydrochloride
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 Hydrochloride

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 ± 3.1 mL/min/kg versus 49.2 ± 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 Nighttime should be stored in tightly closed containers at room temperature (15-30°C).

Others:

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

SPECIAL HANDLING INSTRUCTIONS
Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING
Each Advil® Nighttime liqui-gel, contains 200 mg ibuprofen (as acid and potassium salt) and 25 mg diphenhydramine hydrochloride.

Non-medicinal ingredients: coconut oil, D&C red no. 33, FD&C blue no. 1, gelatin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, sorbitol.

The liqui-gels are available in blister packages of 20 and bottles of 40 liqui-gels.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Ibuprofen

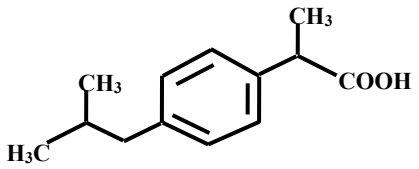
Proper name: Ibuprofen

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

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

Molecular formula and molecular mass: $C_{13}H_{18}0_2$
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: 75–77°C

Diphenhydramine Hydrochloride [130]

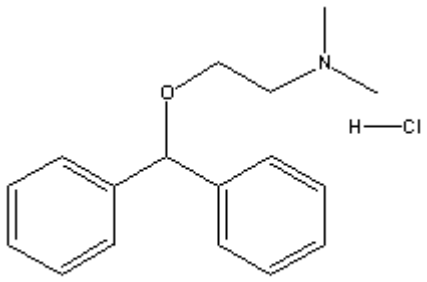
Proper name: Diphenhydramine hydrochloride

Chemical name: O-benzhydryldimethylaminoethanol hydrochloride

Other names: N-dimethylethylamine hydrochloride; 2-(diphenylmethoxy)-N,N-dimethylethanamine hydrochloride

Molecular Formula and molecular mass: $C_{17}H_{21}NO \cdot HCl$

Structural Formula:



Physical characteristics: White, odourless, crystalline powder which slowly darkens on exposure to light.

Solubility: Solublity of 1 g/mL in water and 0.5 g/mL in alcohol at 25ºC

pKa value: pKa = 9

Melting Point: 166º-170ºC

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
Published studies have documented that diphenhydramine is effective for relieving occasional sleeplessness [17]. Clinical trials have shown that single doses of 50 mg or 150 mg of diphenhydramine is comparable to 60 mg pentobarbital as a hypnotic [17].

Studies with Ibuprofen and Diphenhydramine Hydrochloride

The efficacy of Advil Nighttime Liqui-Gels was shown in three Oral Surgery clinical trials (AE-98-01, AE-98-02, AE-04-14A) in subjects, from 16 to 45 years of age, who had undergone surgical removal of one or more impacted third molars at least one of which was a partial bony mandibular impaction and, if two molars were extracted, the other was the corresponding maxillary molar. Each was a randomized, inpatient, placebo-controlled,double-blind, parallel group single centre study in which subjects received a single dose of study medication in the evening of the day of surgery. Subjects were housed in a clinic overnight and were required to go to bed earlier than usual. There was sleep phase advancement to enhance model sensitivity, where subjects dosed and went to bed when they had at least moderate pain, between approximately 6:30 and 8:00 PM which was at least 3 hours earlier than their usual time to retire.

Study AE-98-01, which involved 281 subjects, showed that the combination of ibuprofen 400 mg / diphenhydramine hydrochloride 50 mg and ibuprofen 400 mg alone were both effective in reducing the time to fall asleep within 60 minutes (sleep latency), relieving pain and enhancing sleep compared to placebo [123]. This difference between the two treatment arms and placebo was also seen for the 2-hour time-weighted sum of pain relief and pain intensity (SPRID2) scores which were 1.3, 7.7 and 7.7 for placebo, ibuprofen 400 mg/diphenhydramine hydrochloride 50 mg and ibuprofen 400 mg, respectively. The results for the primary efficacy variables are presented in Table 4. Also, ibuprofen 400 mg / diphenhydramine hydrochloride 50 mg showed a significantly longer duration of sleep compared to ibuprofen 400 mg (Table 5). This was based on an ordered categorical time scale which divided sleep duration into: < 5 hours, 5-6 hours, 6-7 hours, 7-8 hours, 8-9 hours, and > 9 hours and sleep duration was obtained by asking patients the next morning “how many hours did you sleep?”

Table 4. AE-98-01: Advil Nighttime Oral Surgery Study I
Primary Efficacy Parameters: Sleep & Pain (Intent-to-Treat Subjects) [122]

	Placebo N=40	IBU400/DPH50 N=122	IBU400 N=118	Root Mean Square Error	p-values Trt@	Trt*Gender$	Trt*Base&
Cumulative % Asleep at 60 min+							
Number (%)	16 (40.0%)	78 (63.9%)	76 (64.4%)	N/A	0.014*	0.786	0.403
SPRID2++							
MEAN	1.33	7.67	7.63	4.164	< 0.001*	0.207	0.656
STD	3.02	4.26	4.39				
MEDIAN	0.00	8.00	8.00				
RANGE	(-2, 10)	(-2, 14)	(-2, 14)				

Pairwise Comparison p-values@

	IBU400/DPH50 vs. Placebo	IBU400/DPH50 vs. IBU400	IBU400 vs. Placebo
Cumulative % Asleep at 60 min+	0.008F	0.915	0.006f
SPRID2++	< 0.001F	0.952	< 0.001f

*: p ≤ 0.05 for treatment effect or p ≤ 0.15 for interaction effects.
+: @: p-values from the Cochran-Mantel-Haenszel test, controlling for baseline PSR and gender.
$, &: The interactions p-values from the pseudo-homogeneity Cochran-Mantel-Haenszel test using the method of Koch et.al., Statistical Methodology in the Pharmaceutical Sciences Chapter 13:405-406, 1990, edited by Berry.
++: @: p-values from ANOVA model with treatment, baseline PSR, and gender terms.
$: p-value from the addition of trt-by-gender interaction to the model in @.
&: p-value from the addition of trt-by-baseline PSR interaction to the model in @.
The pairwise comparisons were tested sequentially in the order displayed (see section VII.D.4 of report).
F: First treatment significantly better at 0.05 level.
f: First treatment significantly better than second but technically ineligible.
S: Second treatment significantly better at 0.05 level.
s: Second treatment significantly better than first but technically ineligible.

Table 5. AE-98-01: Advil Nighttime Oral Surgery Study I
Duration of Sleep (Intent-to-Treat Subjects) [122]

	Placebo N=40	IBU400/DPH50 N=122	IBU400 N=118	Root Mean Square Error	p-values Trt@	Trt*Gender&	Trt*Ba
<5 hours(0)	34 (85.0%)	30 (25.2%)	37 (31.6%)				
5 to 6 hours(1)	4 (10.0%)	13 (10.9%)	21 (17.9%)				
6+ to 7 hours(2)	0 (0%)	7 (5.9%)	10 (8.5%)				
7+ to 8 hours(3)	1 (2.5%)	12 (10.1%)	7 (6.0%)				
8+ to 9 hours(4)	1 (2.5%)	11 (9.2%)	9 (7.7%)				
>9 hours(5)	0 (0%)	46 (38.7%)	33 (28.2%)				
Missing	0	3	1				
MEAN	0.28	2.83	2.25	1.930	< 0.001*	0.624	0.678
STD	0.82	2.10	2.08				
MEDIAN	0.00	3.00	2.00				
RANGE	(0, 4)	(0, 5)	(0, 5)				

Pairwise Comparisons

p-values	IBU400/DPH50 vs. Placebo	IBU400/DPH50 vs. IBU400	IBU400 vs. Placebo
ANOVA@	< 0.001F	0.022F	< 0.001F
CMH@@	< 0.001F	0.042F	< 0.001F

*: p ≤ 0.05 for treatment effect or p ≤ 0.15 for interaction effects.
@: p-value from ANOVA model with treatment, baseline PSR, and gender terms.
&: p-value from the addition of treatment-by-gender interaction to the ANOVA model in @.
$: p-value from the addition of treatment-by-baseline PSR interaction to the ANOVA model in @.
@@: p-value from CMH, controlling for baseline PSR and gender, using modified ridit scores.
The pairwise comparisons (1) and (2) were tested sequentially; (3) was presented for completeness.
F: First treatment significantly better than second at 0.05 level.
f: First treatment significantly better than second but technically ineligible.
S: Second treatment significantly better than first at 0.05 level.
s: Second treatment significantly better than first but technically ineligible.
Note: Percentages are based on non-missing data.

The second study, AE-98-02, involved 283 subjects and showed that the ibuprofen 400 mg / diphenhydramine 50 mg and ibuprofen 400 mg alone were both effective in reducing the time to fall asleep (sleep latency), relieving pain and enhancing sleep compared to placebo [124]. The study also showed that the mean scales (5-point scale) for the duration of sleep were 0.05, 2.61 and 1.98 in the placebo, ibuprofen 400 mg / diphenhydramine 50 mg and ibuprofen 400 mg respectively. The cumulative percentage of subjects who had fallen asleep by 60 minutes in the corresponding groups was 27.5%, 66.4% and 75.6% and the 2-hour SPRID scores were 0.3, 7.0 and 7.8. Both ibuprofen 400 mg/ diphenhydramine 50 mg, and the ibuprofen 400 mg dose groups were significantly better than placebo for both sleep parameters as well as the pain parameter. With respect to the comparison of the two actives, ibuprofen 400 mg / diphenhydramine 50 mg, subjects experienced a significantly longer sleep duration than the ibuprofen 400 mg subjects (p=0.005). The results for the primary efficacy variables are presented in Table 6 [124]. For this study, as was the case for study AE-98-01 above, sleep duration was assessed on an ordered categorical time scale which divides sleep duration into: < 5 hours, 5-6 hours, 6-7 hours, 7-8 hours, 8-9 hours, and >9 hours and sleep duration was obtained by asking patients the next morning, "how many hours did you sleep?"

Table 6. AE-98-02: Advil Nighttime Oral Surgery Study II
Primary Efficacy Parameters: Sleep & Pain (Intent-to-Treat Subjects) [123]

	Placebo N=40	IBU400/DPH50 N=119	IBU400 N=123	Root Mean Square Error	p-values Trt@	Trt*Gender$	Trt*Base&
Duration of Sleep+							
<5 hours(0)	39 (97.5%)	26 (21.8%)	41 (33.3%)				
5 to 6 hours(1)	0 (0%)	18 (15.1%)	18 (14.6%)				
6+ to 7 hours(2)	1 (2.5%)	12 (10.1%)	15 (12.2%)				
7+ to 8 hours(3)	0 (0%)	12 (10.1%)	14 (11.4%)				
8+ to 9 hours(4)	0 (0%)	23 (19.3%)	22 (17.9%)				
>9 hours(5)	0 (0%)	28 (23.5%)	13 (10.6%)				
MEAN	0.05	2.61	1.98	1.711	< 0.001*	0.885	0.424
STD	0.32	1.92	1.81				
MEDIAN	0.00	3.00	2.00				
RANGE	(0, 2)	(0, 5)	(0, 5)				
Cumulative % Asleep at 60 min++							
Number (%)	11 (27.5%)	79 (66.4%)	93 (75.6%)	N/A	< 0.001*	0.405	0.619
SPRID2+							
MEAN	0.26	7.03	7.81	3.012	< 0.001*	0.966	0.962
STD	2.07	3.47	2.87				
MEDIAN	0.00	7.00	8.00				
RANGE	(-2, 6)	(-2, 14)	(-2, 14)				

*: p ≤ 0.05 for treatment effect or p ≤ 0.15 for interaction effects.
+: @: p-values from ANOVA model with treatment, baseline PSR, and gender terms.
$: p-value from the addition of trt-by-gender interaction to the model in @.
&: p-value from the addition of trt-by-baseline PSR interaction to the model in @.
++: @: p-values from the Cochran-Mantel-Haenszel test, controlling for baseline PSR and gender.
$, &: The interactions p-values from the pseudo-homogeneity Cochran-Mantel-Haenszel test using the method of Koch et.al., Statistical Methodology in the Pharmaceutical Sciences Chapter 13:405-406, 1990, edited by Berry.

The third study, AE-04-14A [125] involved 329 subjects, of whom 165 took ibuprofen (400mg)/diphenhydramine (50 mg) and 164 who took ibuprofen (400 mg) alone. There was no placebo group. The combination 400 mg ibuprofen / 50 g diphenhydramine hydrochloride was found to be more effective than 400 mg ibuprofen alone for improving sleep duration. In this study sleep duration was measured with an actigraph as well as by the subjective assessment of subjects. In addition, this study showed that the combination significantly improved sleep efficacy and reduced the time awake after sleep onset compared to treatment with ibuprofen alone. Although pain relief was not assessed directly, this study showed that the combination product also reduced the need for rescue medication compared to treatment with ibuprofen alone.

DETAILED PHARMACOLOGY

Ibuprofen

Animal Pharmacology

Cyclooxygenase inhibitors such as ibuprofen and other NSAIDs reduce thromboxane A_2 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_2 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^{14}-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 at 2-4', (2-hydroxy-2-methylpropyl) phenylpropionic acid (metabolite A) and 2-4' (2-carboxpropyl) phenylpropionic acid (metabolite B). About 1/3 of the dose was excreted in the urine of patients as metabolite B, 1/10 as unchanged ibuprofen and 1/10 as metabolite A. The remainder of the dose could not be identified in the urine [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.

Diphenhydramine Hydrochloride

Human Pharmacology
Seven intensive care patients were studied for the effects of cimetidine, an H2 antagonist on cardiovascular parameters with and without premedication. Cimetidine 200 mg was administered IV on Day 1. Mean artial pressure dropped within 2 minutes and remained below baseline for the 8 minute measurement period. Diphenhydramine, an H1 antagonist, was administered as 40 mg IV 5 minutes before administering cemetidine 200 mg IV on day 2. Mean arterial pressure did not change. The authors concluded that cemetidine has enough H1-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_{50} values for ibuprofen in mice and rats, expressed as mg/kg of body weight, are as follows:

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

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

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

The LD_{50} value for diphenhydramine hydrochloride in rats is 500 mg/kg [135].

Reproduction studies in rats and rabbits receiving diphenhydramine hydrochloride dosages up to five times the recommended human dosage have not revealed evidence of harm to the fetus or impaired fertility [16].

Ibuprofen and Diphenhydramine Hydrochloride

Acute Toxicity Studies [113]

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

		LD_{50}
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 proprionic 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.[140, 141] 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.[142] A recent study in mouse bone marrow cells suggested a potential for chromosomal aberrations after oral dosing.[143] 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.[144]

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^{14} labelled ibuprofen. Rabbits were killed three hours after dosing and rats killed 1.5 hours after dosing when maternal and foetal blood was collected. Similar concentrations of radioactive ibuprofen were detected in both the mother and foetus indicating that the drug and its metabolites readily crossed the placental barrier into the foetal circulation.[145]

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PART III: CONSUMER INFORMATION

Advil Nighttime
Ibuprofen 200 mg / Diphenhydramine Hydrochloride 25 mg capsules

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

ABOUT THIS MEDICATION

- For fast and effective temporary relief of occasional mild to moderate nighttime pain and accompanying sleeplessness, due to minor aches and pains associated with joints, muscles, backache, headache and toothache as well as pain of migraine and arthritis.

- For longer sleep, uninterrupted by temporary pain.

Only for temporary mild to moderate pain that causes sleeplessness. If this is not the case, do not use.

What it does:
Contains two drugs: ibuprofen (a pain reliever for short term use) and diphenhydramine hydrochloride (a sleep-aid for sleeplessness). Pain relief from ibuprofen helps to fall asleep, and diphenhydramine helps to stay asleep.

When it should not be used:
Do not use if:

- You 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 Nighttime ingredients (Refer to the nonmedicinal ingredients on outer carton or composition section)
- You have pain that does not keep you from sleeping.
- You have sleeplessness but are not in pain.
- You have active or recurrent stomach ulcer, gastrointestinal (GI) bleeding, or active inflammatory bowel disease (e.g. Crohn's, colitis).
- You have 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
- You have serious liver or kidney disease
- You have high potassium in the blood
- You are taking, ASA, acetaminophen, or other NSAIDs, such as naproxen or other ibuprofen product, antihistamines and or diphenhydramine containing products, (e.g. for cough & cold, sleep aids, etc.),
  monoamine oxidase inhibitors (MAOIs)
- You are dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake
- You have heart problems, such as high blood pressure or severe coronary artery disease,
- right before or after heart surgery,
- You have System Lupus Erythematosus,
- You are in your third trimester of pregnancy.

What the medicinal ingredients are:
Ibuprofen and diphenhydramine hydrochloride.

What the nonmedicinal ingredients are:
Coconut oil, D&C red no. 33, FD&C blue no. 1, gelatin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, and sorbitol.

What dosage forms it comes in:
Each Liqui-Gel (gelatin capsule) contains ibuprofen 200 mg (as free acid and potassium salt) and diphenhydramine hydrochloride 25 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Causes sedation or sleepiness. Not for daytime use.
Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcers. 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 acetylsalicyclic acid (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.
Advil Nighttime should not be used during the third trimester of pregnancy.
Talk to your doctor if you are trying to conceive, in your first or second trimester of pregnancy or if breastfeeding
Stop use immediately if you have difficulty or pain when urinating.

BEFORE use, talk to your doctor or pharmacist if you have/are:

- 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
- Autoimmune disease (e.g. lupus)
- High blood pressure

• Over 65 years of age
• You are trying to conceive, pregnant or breastfeeding.
• Sleeplessness due to mild to moderate pain persists continually for more than 5 days.

Insomnia may be a symptom of a serious underlying medical condition other than pain.

While taking this product, do not drive motor vehicle or operate machinery.

Use with caution in the elderly

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

The use of NSAIDs, like Advil Nighttime in the second trimester of pregnancy should be restricted to the lowest dose necessary for the shortest possible duration.

At 20 weeks or later in pregnancy, your use of NSAIDs may need to be monitored by a doctor due to the rare risk of kidney problems in the unborn baby which may result in decreased amniotic fluid volume and other complications.

Stop use and ask a doctor if
• you show signs of stomach bleeding
• pain worsens or lasts more than 5 days
• fever worsens or lasts more than 3 days
• any new symptoms appear

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 preventive benefits of ASA.**

Drugs that may interact with Advil Nighttime 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), tranquilizers, alcohol or other sedating drugs, NSAIDs (including naproxen and ibuprofen), sleep-aids, cold medications

Do not take this product at the same time as other medications containing pain relievers (e.g., ibuprofen, ASA, acetaminophen, naproxen, etc.) or diphenydramine (e.g., allergy medications, sedating drugs, cough/cold/flu medications, antinausea drugs) etc.

PROPER USE OF THIS MEDICATION

Usual dose:
Adults and children 16 to 65 years: Take a single dose of 1 or 2 Liqui-Gels at night. Do not take more than the recommended dosage unless directed by a physician. Do not exceed 1200 mg of ibuprofen and 300 mg of diphenhydramine (including the 200-400 mg ibuprofen and 25-50 mg diphenhydramine hydrochloride from Advil Nighttime dose) in 24 hours. Should be taken no sooner than 4-6 hours after the last daytime ibuprofen or diphenhydramine dose. See ***Interactions with this Medication*** for examples of other products which contain these ingredients. Do not take for more than 5 consecutive nights unless directed by a physician.

Do not give to children under 16 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: stop use and contact a health care practitioner, hospital emergency department, or poison control centre immediately, even if there are no

Missed Dose:
Take once at night before bedtime. Do not take twice the recommended dose after 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 oritching, 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 Nighttime discontinue use immediately and contact a physician.

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

Consult your physician if the symptoms of pain or sleeplessness persist for more than 5 days.

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

STOP USE and consult your physician immediately if you experience: abdominal pain, allergic reaction (itching, blisters, rashes, skin reddening, etc), any change in vision, blood in vomit, bloody or black stools, bladder pain, hallucinations, or difficulty speaking.

T*his is not a complete list of side effects. For any unexpected effects while taking Advil Nighttime, contact your doctor or pharmacist.*

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/reportdeclaration/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).

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 found by contacting the sponsor, GlaxoSmithKline Consumer Healthcare Inc., Mississauga, ON L5N 6L4 at: 1-888-275-9938.

This leaflet was prepared by GlaxoSmithKline Consumer Healthcare Inc.

Product monograph available to physicians and pharmacists upon request.

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