PRODUCT MONOGRAPH

NIGHTTIME PAIN RELIEVER

Ibuprofen and Diphenhydramine Hydrochloride Liquid Gel Capsules

Ibuprofen 200mg and Diphenhydramine Hydrochloride 25mg

Analgesic/Sleep Aid

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Liquid Gel capsules: 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

Nighttime Pain Reliever (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.

Nighttime Pain Reliever 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 Nighttime Pain Reliever in this population should only be recommended after evaluation on an individual basis for sleeplessness due to acute pain by a physician.

Pediatrics (<16 years of age):
Nighttime Pain Reliever 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.
- Significant hepatic impairment or active liver disease.
- Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.
- Ibuprofen is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.
- 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 should not be used during pregnancy or by nursing mothers.
- Ibuprofen is contraindicated in patients with systemic lupus erythematosus, as an anaphylaxis-like reaction with fever may occur, particularly when ibuprofen has been administered previously.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Use with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention (See *WARNINGS AND PRECAUTIONS, Cardiovascular and Fluid and Electrolyte Balance; and DRUG INTERACTIONS, Antihypertensives*).
- Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer (See *WARNINGS AND PRECAUTIONS, Gastrointestinal DRUG INTERACTIONS, Coumarin-type anticoagulants*).
- Patients at greatest risk of renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly (See *WARNINGS AND PRECAUTIONS, Renal*).
- If urinary symptoms, hematuria and cystitis occur, the drug should be stopped immediately (See *WARNINGS AND PRECAUTIONS, Genitourinary*).
- Ibuprofen use during pregnancy/nursing should be avoided (See *WARNINGS AND PRECAUTIONS, Special Populations: Pregnant Women and Nursing Women*).
- Nighttime Pain Reliever causes sedation or sleepiness. Not for daytime use**.**

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

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, a physician should be consulted.

Carcinogenesis and Mutagenesis
Not applicable.

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

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 Nighttime Pain Reliever (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. Nighttime Pain Reliever 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 gastrointestinal (GI) toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with NSAIDs including ibuprofen.

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

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

Nighttime Pain Reliever 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, Nighttime Pain Reliever should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anticoagulant use have been associated with increased risk. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

There is no definitive evidence that the concomitant administration of histamine H2- receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of Ibuprofen and Diphenhydramine Hydrochloride Capsule 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 Nighttime Pain Reliever must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

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

Hematologic
Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when ibuprofen is administered.

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.

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. 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 Nighttime Pain Reliever Capsule.

Peri-Operative Considerations

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

Psychiatric

See *Warnings and Precautions, Neurologic*.

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

Renal
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 the renal 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 Nighttime Pain Reliever 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].

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
Not applicable.

Special Populations
Pregnant Women:

Ibuprofen: Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of

human response. Because of the known effects of NSAIDs on the fetal cardiovascular system, use of ibuprofen during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of ibuprofen is not recommended during pregnancy (Also see *Contraindications)*.

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

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

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].

Pediatrics: Studies conducted to date have not demonstrated pediatric-specific problems that would limit the usefulness of ibuprofen in children 6 months and older.

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. 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 [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 *Warnings and Precautions* related to the use of Nighttime Pain Relieverand Monitoring and Laboratory Tests see *Fluid and Electrolyte Balance*, *Gastrointestinal*, *Hematologic*, *Hepatic*, *Renal* and *Subpopulations: Elderly*.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse reaction rates

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

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 Ibuprofen and Diphenhydramine Hydrochloride Capsules (ibuprofen 200 mg/diphenhydramine HCl 25 mg) (n= 158),or two Ibuprofen and Diphenhydramine Hydrochloride Capsules (ibuprofen 400 mg/diphenhydramine HCl 50 mg) (n=323), or two Tylenol PM caplets (acetaminophen 1000 mg/diphenhydramine HCl 50 mg) (n=326) or a placebo (N=167) for 10 consecutive evenings. They were instructed to begin taking the study drug on the first evening they experienced sleeplessness associated with a headache or minor aches or pains. They continued to take study medication for the next 9 consecutive evenings, regardless of whether or not they were experiencing symptoms. Although the duration of use was beyond the maximum over-the-counter duration of use (10 days versus 5 days) of ibuprofen, the daily dose was below the maximum daily dose for ibuprofen of 1200 mg and for diphenhydramine of 150 mg. The study suggests that there are no clinically relevant safety concerns associated with Ibuprofen and Diphenhydramine Hydrochloride Capsules 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 and Diphenhydramine Hydrochloride Capsules 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[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. Ibuprofen and Diphenhydramine Hydrochloride Capsule (n=158)**	**2. Ibuprofen and Diphenhydramine Hydrochloride Capsules (n=323)**	**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 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, and 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 0.05; b: Marginally significant (0.05 < p 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 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. When used as directed to treat pain, non-prescription ibuprofen at the maximum dose of 1200 mg/day for 10 days, is well tolerated.

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. Reports from spontaneous reporting systems in the United Kingdom [138], France and the United States [139], where a prescription is not needed for ibuprofen at a daily dose up to 1200 mg, confirm the medication's gastrointestinal safety and acceptability.

A 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: ASA 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 ASA (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 ASA [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). Any patient with eye complaints during ibuprofen therapy should have an ophthalmological examination. Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

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

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

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.

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

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.
Fluid retention generally responds promptly to drug discontinuation (See WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Serious Drug Interactions

- 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 acetaminophen may increase the risk of adverse renal effect.
- 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

Nighttime Pain Reliever is not recommended for concomitant use with any other NSAIDs, including ASA. Documented or possible drug interactions with Ibuprofen and Diphenhydramine Hydrochloride Capsule 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 Nighttime Pain Reliever Capsule is not advisable: it may increase the risk of adverse renal effect.

Acetylsalicylic acid (ASA) or other NSAIDs

The use of Nighttime Pain Reliever in addition to any other NSAID, including ASA, is not recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects. Animal studies show that ASA given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood

levels of the non-ASA drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of ASA 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. [141].

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 Nighttime Pain Reliever Capsule. (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, chronic glaucoma and altered mental status [17].

Caution is necessary if Nighttime Pain Reliever Capsule 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 hydrochlorothiazide and fosinopril who received ibuprofen 2400 mg/day for one month [82]. [63]. 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 Nighttime Pain Reliever Capsule 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 Nighttime Pain Reliever Capsule is not advisable: it may increase the risk.

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 (e.g., cyclosporine), phenytoin, corticosteriods or benzodiazepines.

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

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

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

Drug-Lifestyle-Interactions
No lifestyle parameters are suggested for the use of Nighttime Pain Reliever.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Do not take for pain for more than 5 days unless directed by a physician.

The safety issues to consider when developing a dosage regimen of Nighttime Pain Reliever for individual patients is applicable to:

Elderly patients older than 65 years who are frail or debilitated and consideration should be given to a starting dose lower than the one usually recommended (see WARNINGS AND PRECAUSTIONS, Elderly).

Recommended Dose and Dosage Adjustment

Adults ≥16 to 65 years of age: Take a single dose of 1 or 2 soft gelatin capsules, 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 Nighttime Pain Reliever dose) and 300 mg diphenhydramine (including the 25-50 mg from Nighttime Pain Reliever dose, if this is being taken during the day as an antihistamine) in 24 hours. Nighttime Pain Reliever can be taken 4 hours after the last ibuprofen and/or diphenhydramine dose. Do not recommend Nighttime Pain Reliever use for more than 5 consecutive nights without evaluating the causes for sleeplessness with pain.

Missed Dose

Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and skip the missed dose. Do not take twice the recommended dose after a missed dose.

Administration

See *Recommended Dose and Dosage Adjustment*.

OVERDOSAGE

Symptoms of Overdosage

Nighttime Pain Reliever 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 arrhythmias. Cardiac arrhythmias are similar to those following an overdose of other drugs and class Ia antiarrhythmic properties and result from the blockade of fast sodium channels [129,131].

Treatment of Overdosage

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.

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

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

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

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.

In children, ibuprofen overdoses less than 100 mg/kg are unlikely to produce toxicity. In adults, the dose of ibuprofen reportedly ingested does not appear to be predictive of toxicity.

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

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

Nighttime Pain Reliever should be stored in tightly closed containers at room temperature (15-30^{o}C).

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

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each Nighttime Pain Reliever soft gelatin capsule, contains 200 mg ibuprofen (as acid and potassium salt) and 25 mg diphenhydramine hydrochloride.

Nighttime Pain Reliever soft gelatin capsules, violet colored oval shaped capsules liquid filled containing colorless to violet colored, transparent, viscous liquid, printed ‘162’ in white color on capsule shell. Available in blister packages of 4x10’s and bottles of 10’s and 100’s.

Non-medicinal ingredients: Polyethylene glycol, Povidone K-30, Potassium hydroxide, Purified water, gelatine, special sorbitol sorbitan solution, FD& C Blue No. 1, D& C red No. 33, isopropyl alcohol, pharmaceutical ink.

PART II: SCIENTIFIC INFORMATION

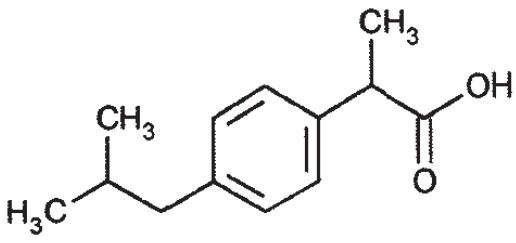
PHARMACEUTICAL INFORMATION

Drug Substance

Ibuprofen

Proper name:	Ibuprofen
Chemical name:	(±)-2-(p-isobutylphenyl) propionic acid
Other names:	Benzeneacetic acid; A-methyl-4-(2-methylpropyl), (±) (±)-p-isobutylhydratropic acid Brufen
Molecular formula and molecular mass:	$C_{13}H_{18}O_2$ 206.28 daltons

Structural formula:



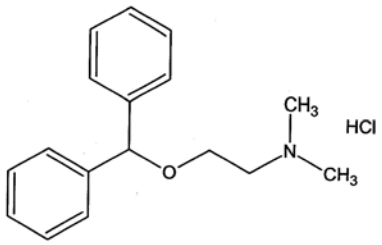
Physical characteristics:	White to off-white crystalline powder having a slightly characteristic odor.
Solubility:	Practically insoluble in water, very soluble in alcohol, in acetone, in methanol & in chloroform; slightly soluble in ethyl acetate.

Diphenhydramine Hydrochloride [130]

Proper name:	Diphenhydramine hydrochloride
Chemical name:	Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-hydrochloride 2-(Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride

Molecular Formula and molecular mass: $C_{17}H_{21}NO \cdot HCl$, 291.82

Structural Formula:



Physical characteristics:	A white, odorless, crystalline powder. Slowly darkens on exposure to light.
Solubility:	Freely soluble in water, alcohol, & chloroform; sparingly soluble in acetone; very slightly soluble in benzene& ethyl ether.

Solubility of 1 g/mL in water and 0.5 g/mL in alcohol at 25ºC pKa value:
pKa = 9

Melting Point:	167º-172ºC

CLINICAL TRIALS

Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study of Nighttime Pain Reliever (ibuprofen/diphenhydramine hydrochloride 200mg/25mg) soft gelatin capsules (Marcan Pharmaceuticals Inc.) and Advil Nighttime Liqui-Gels® (ibuprofen/diphenhydramine hydrochloride 200mg/25 mg) (Wyeth Consumer Healthcare Inc.) was conducted in 25 healthy, adult, Asian male and female subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Ibuprofen (1 x 200 mg ibuprofen/25mg diphenhydramine hydrochloride) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (µg*hr/mL)	56.6 57.7 (22.2)	55.8 56.9 (20.9)	101.4	98.6- 104.3
AUC_{0-inf} (µg*hr/mL)	58.8 60.1 (22.2)	57.7 58.8 (20.7)	102.0	99.2- 104.8
C_{max} (µg/mL)	18.6 19.4 (28.3)	18.2 18.7 (25.1)	102.5	90.5- 116.1
T_{max} € (h)	1.5 (54.0)	1.6 (68.3)		
$T_{½}$ € (h)	2.0 (19.4)	1.9 (19.8)		

* Nighttime Pain Reliever (ibuprofen/diphenhydramine hydrochloride 200 mg/ 25mg) soft gelatin capsules (Marcan Pharmaceuticals Inc).

† Advil Nighttime Liqui-Gels® (ibuprofen/diphenhydramine hydrochloride 200 mg/ 25mg) (Wyeth Consumer Healthcare Inc., Canada) were purchased in Canada.

€ Expressed as the arithmetic mean (CV%) only.

Diphenhydramine (1 x 200 mg ibuprofen/25mg diphenhydramine hydrochloride) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (ng*hr/mL)	362.7 377.1 (27.8)	371.2 383.7 (25.0)	97.7	92.6- 103.1
AUC_{0-inf} (ng*hr/mL)	391.3 404.7 (26.5)	396.3 408.5 (24.4)	98.7	93.6- 104.9
C_{max} (ng/mL)	36.9 37.9 (22.8)	38.0 38.9 (20.9)	97.2	92.3- 102.3
T_{max} € (h)	3.3 (36.6)	3.3 (28.7)		
$T_{½}$ € (h)	10.6 (14.9)	10.3 (15.8)		

* Nighttime Reliever (ibuprofen/diphenhydramine hydrochloride 200 mg/ 25mg) soft gelatin capsules (Marcan Pharmaceuticals Inc).

† Advil Nighttime Liqui-Gels® (ibuprofen/diphenhydramine hydrochloride 200 mg/ 25mg) (Wyeth Consumer Healthcare Inc., Canada) were purchased in Canada.

€ Expressed as the arithmetic mean (CV%) only.

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].

Dental Pain
A double-blind, randomized study showed that ibuprofen 400 mg relieved dental pain following removal of impacted third molars significantly better than acetaminophen and placebo [23]. Several other comparative dental studies have described similar results [24-30].

Multiple published studies have demonstrated the efficacy of ibuprofen 400 mg compared to placebo, several different Cyclooxygenase 2 (COX-2) inhibitors, and other NSAIDs in the treatment of patients with moderate or severe pain following the extraction of two or more third molar teeth [26-27, 150-157].

The results of the trials utilized the primary end points of total pain relief at 8 hours (TOTPAR8) [150-152, 155, 156], Pain Intensity Difference (PID) [26, 153], and Sum of Pain Intensity Differences (SPID) [27, 154-155, 157] as pain relief measures. Duration of effect was assessed using the median or mean time (hours) to use rescue medication. Global evaluation of pain relief at 8 hours was also used with subjects asked to report their level of pain relief after 8 hours.

The duration of effect was 8 hours (range from 6 to 10 hours).

In four similar randomized, single dose, placebo and active comparator controlled, parallel group studies, the analgesic efficacy of ibuprofen 400 mg was compared to placebo and various COX-2 inhibitors at different doses [150-152, 156] when treating postoperative dental pain. The studies established that ibuprofen 400 g had median duration of effect (in hours) of 8.9, 10.0, 10.1, and 6.1, respectively, while placebo's median duration of effect was 1.5, 1.6, 2.1 and 2.4, respectively. In all 4 studies, the pain relief measure of TOTPAR8 revealed ibuprofen 400 mg to be statistically significantly superior to placebo with $p<0.001$. In three of the studies, the global evaluation of pain relief at 8 hours was reported and 73%, 74%, and 78% of the ibuprofen 400 mg
patients reported good, very good or excellent pain relief after 8 hours compared to 19%, 7%, and 19% of placebo patients. Median time to onset of pain relief (minutes) was also proven to be statistically significantly different to placebo (>240 minutes) compared to the Ibuprofen 400 mg patients (24, 30, 30 minutes, respectively) [150-152].

In another randomized, single dose, double blind placebo and active comparator controlled, parallel group study, the analgesic efficacy of lumiracoxib 100 (n=51) and 400 mg (n=50) was compared with ibuprofen 400 mg (n=51) and placebo (n=50). The primary endpoint was PID and the secondary measures included time to onset of analgesia and duration of effect. The results

showed the PID scores for ibuprofen 400 mg were statistically superior to placebo across all time points from 1 to 12 hours [153]. Median time to onset of pain relief was 12 hours or more for placebo, 41.5 minutes for ibuprofen, which was statistically significantly different versus placebo. The duration of effect were ~2 hours placebo and ibuprofen ~8 hours ($p<0.001$ vs. placebo) [153].

Several other randomized, single dose, double blind placebo and active comparator controlled, parallel group studies, the analgesic efficacy of ibuprofen 400mg was compared to placebo and various NSAIDs. The studies reported that the duration of analgesic effect, as measured by the median time to use of rescue medication, was 8.5, 5.7, 6.3, 6 and 5.8 hours in patients taking 400mg ibuprofen while placebo duration of analgesic effect was 4.5, 2.8, 2.7, 1.1, 1.4 hours, respectively. The studies utilized either PID, SPID or pain relief combined with pain intensity difference (PRID) pain relief measures. The results all showed that Ibuprofen 400mg groups were statistically significantly different at 8 hours versus placebo ($p<0.05$) [26-27, 154-155, 157]

Muscle Aches
A double-blind, randomized study showed that ibuprofen 400 mg every four hours for a total of three doses relieved muscle soreness following exercise significantly better than acetaminophen 1000 mg and placebo every four hours [31]

Headache
A double-blind, randomized study showed that ibuprofen 400 mg relieved headache pain significantly better than acetaminophen 1000 mg and placebo [20]. Another double-blind, placebo-controlled, randomized study showed that ibuprofen 400 mg began to exert a significant analgesic effect on headache within 30 minutes after dosing [21]. A third double-blind, randomized study confirmed that ibuprofen 400 mg provided significantly faster onset of relief as measured by first perceptible relief, percent attaining complete relief, and superior overall analgesic efficacy compared to acetaminophen 1000 mg for relief of episodic tension-type headache [22].

Dysmenorrhea
Several studies demonstrate the significant effect of ibuprofen compared to placebo or other active analgesics on uterine pain and cramping [32-37].

Fever
The antipyretic efficacy of ibuprofen has been demonstrated in adult fever [38-40].

Pain of Osteoarthritis
Controlled clinical studies in adults provide substantial evidence of the safety and efficacy of ibuprofen at doses of 1200 mg or less per day in relieving the pain of osteoarthritis [148-149]. These studies support an indication for the relief of pain from inflammation associated with conditions including:
- arthritis
- physical or athletic overexertion (e.g. sprains or strains).

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 Ibuprofen and diphehydramine capsules 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: Ibuprofen and Diphenhydramine capsules 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: Ibuprofen and Diphenhydramine capsules 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 5. AE-98-01: Ibuprofen and Diphenhydramine capsules Oral Surgery Study I
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.

Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA (81 – 325 mg per day) on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release ASA dosing, a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

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 arterial 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 cimetidine 200 mg IV on day 2. Mean arterial pressure did not change. The authors concluded that cimetidine 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 propionic acid non-steroidal anti-inflammatory drugs (NSAIDs). Secondary effects included decreased hemograms suggesting GI bleeding, which is a characteristic adverse effect from treatment with NSAIDs. There was no indication that the ibuprofen effect was potentiated by the addition of diphenhydramine. A NOEL was calculated for the drug combination of 25:6.25 mg/kg/day [115].

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

Teratology Studies

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

Overall, ibuprofen induced prototypical GI lesions characterized by erosions and ulcers. In addition, many animals at the higher doses showed renal papillary necrosis and/or edema. Rats and dogs are highly sensitive to NSAIDs compared to humans and, therefore, presented with these findings. Diphenhydramine is an antihistaminic drug with sedative properties. Animals given the high doses of this drug showed darkening or reddening of the major organs in the thorax and abdomen. The cause of these findings may result from physiologic depression resulting in decreased blood circulation with stasis occurring in these tissues. Rats who received diphenhydramine in the acute studies usually died within the first day or so after dosing, earlier than rats given ibuprofen. There was no indication of drug:drug interaction in any of the studies with the proposed combination drug product.

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PART III: CONSUMER INFORMATION

Nighttime Pain Reliever

Ibuprofen and Diphenhydramine Hydrochloride Liquid Gel Capsules

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

ABOUT THIS MEDICATION

What the medication is used for:

Nighttime Pain Reliever

For fast and effective 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).

When it should not be used:

Do not use if:

- You have active peptic ulcer, a history of recurrent ulceration active inflammatory disease of the gastrointestinal system or gastrointestinal bleeding.
- Nasal polyps (swelling of the inside of the nose), or allergic manifestations such as asthma, anaphylaxis (sudden severe life threatening allergic reaction), uticaria/hives, rhinitis (stuffed or runny nose that may be due to allergies), skin rash or other allergic symptoms,
- Taking, acetylsalicylic acid (ASA), acetaminophen, or other Non-Steroidal Anti-inflammatory Drugs (NSAIDs), such as naproxen or other ibuprofen product.
- Known or suspected hypersensitivity or allergy to ibuprofen or other NSAIDs, ASA or other salicylates, diphenhydramine or to any ingredient in the formulation.
- Dehydrated (significant fluid loss) due to vomiting, diarrhea or lack of fluid intake.
- Diagnosed with severe high blood pressure or have severe coronary artery disease, serious liver or kidney disease, Systemic Lupus Erythematosus.
- Pregnant or nursing.
- You have pain that does not keep you from sleeping.
- You have sleeplessness but are not in pain.

What the medicinal ingredients are:

Ibuprofen (present as free acid and potassium slat) and diphenhydramine hydrochloride.

What the nonmedicinal ingredients are:

Polyethylene glycol, Povidone K-30, Potassium hydroxide, Purified water, gelatine, special sorbitol sorbitan solution, FD& C Blue No. 1, D& C red No. 33, isopropyl alcohol and pharmaceutical ink.

What dosage forms it comes in:

Each soft gelatin capsule (gelatin capsule) contains ibuprofen 200 mg (as free acid and potassium salt) and diphenhydramine hydrochloride 25 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings And Precautions

- Caution in patients prone to gastrointestinal tract irritation, including those with a history of peptic ulcer.
- Nighttime Pain Reliever causes sedation or sleepiness. Not for daytime use.

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

- Diabetes
- Chronic lung disease
- Glaucoma
- Difficulty in urination due to an enlarged prostate
- Autoimmune disease (e.g., lupus)
- High blood pressure
- Heart disease
- Heart failure or thyroid disease
- Peptic ulcers
- Asthma
- Blood clotting disorders (such as hemophilia)
- Kidney or liver disease
- Any other serious disease
- Taking any other prescription or over-the-counter drug
- Over 65 years of age
- Pregnant or nursing a baby
- 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.

INTERACTIONS WITH THIS MEDICATION

Do not use Nighttime Pain Reliever if you are taking:

- Daily low dose ASA (81-325mg), without taking to a doctor or pharmacist. Ibuprofen may interfere with the preventive benefits of ASA.
- ASA or other anti-inflammatory medication.

Drugs that may interact with Nigttime Reliever include:

- Anticoagulants (blood thinners)
- Antihistamines, tranquilizers, alcohol or other sedating drugs
- Digoxin
- Diuretics (e.g., for bloating or heart conditions)
- Insulin
- Lithium
- Medications for high blood pressure or depression, including mononamine oxidase inhibitors (MAOIs)
- Methotrexate
- Oral antidiabetic agents
- Other NSAIDs
- Other pain relievers, sleep-aids or cold medicines
- Protien-bound drugs including probenecid, thyroxine, antibiotics, phenytoin, corticosteroids or benzodiazapenes.

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.

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

PROPER USE OF THIS MEDICATION

Usual dose:
Adults ≥ 16 to 65 years: Take 1 or 2 capsules at night, 4-6 hours after the last daytime ibuprofen or diphenhydramine dose. Do not take more than 5 consecutive days/nights unless directed by a doctor. **Do not exceed a combined total of any 6 Nighttime Pain Relievers in 24 hours, unless directed by a doctor.**

Do not give to children under 16 unless directed by a doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take your medicine and

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If heartburn, nausea or vomiting, bloating, diarrhea or constipation, ringing or buzzing in the ears, nervousness, dizziness, fluid retention, or any other side effect or unexplained symptoms develop while taking Nighttime Pain Reliever, discontinue use immediately and contact a doctor.

Talk to your doctor if the symptoms of pain or sleeplessness persist for more than 5 days.

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

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

STOP USE and consult your doctor 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.

This is not a complete list of side effects. For any unexpected effects while taking Nighttime Pain Reliever, contact your doctor or pharmacist.

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.

REPORTING SUSPECTED SIDE EFFECTS

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

Report online at www.healthcanada.gc.ca/medeffect

- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Marcan Pharmaceuticals Inc. at: 1-613-228-2600

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