PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

ALEVE® NIGHTTIME

Naproxen Sodium and Diphenhydramine Hydrochloride
Tablets, 220 mg /25 mg, Oral
Non-steroidal anti-inflammatory drug (NSAID), Analgesic and Sleep Aid

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	10/2025
8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions	10/2025
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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

ALEVE® NIGHTTIME (Naproxen Sodium and Diphenhydramine Hydrochloride Tablet) is a non-prescription analgesic and sleep aid preparation to be taken as a single dose of 2 tablets at bedtime. ALEVE® NIGHTTIME is indicated for:

- Occasional use, for a limited period of time (five days or less), for fast and effective relief of acute nighttime pain and accompanying sleeplessness caused by aches and pains associated with arthritis, joints, muscles, backache, headache, migraine pain and toothache and, in these circumstances, for increased duration of sleep uninterrupted by pain
- Helps you fall asleep and stay asleep

1.1 Pediatrics

Children under 12 should not take this drug, unless directed by a doctor. The safety in pediatric use has not been established (See 7 WARNINGS AND PRECAUTIONS).

1.2 Geriatrics

Patients older than 65 years and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. 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 esophageal injury including ulceration and bleeding.
The elderly are also more susceptible to the side effects of diphenhydramine.
For such patients, considerations should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision. (See 7 WARNINGS AND PRECAUTIONS).

2. CONTRAINDICATIONS

ALEVE® NIGHTTIME is contraindicated in patients:

- who have previously exhibited allergy or with known hypersensitivity to the active substances naproxen (including naproxen sodium) or diphenhydramine hydrochloride or any of the excipients in the tablet. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section
- with a history of asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid (ASA) or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. 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 reaction.

- with active peptic ulcers, a history of recurrent ulceration, or active gastrointestinal bleeding
- with inflammatory bowel disease.
- with severe liver impairment or active liver disease
- with severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored)
- in women in their third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and prolonged parturition
- right before or after heart surgery
- with any other product containing diphenhydramine, even one used on skin

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Risk in Pregnancy*: Caution should be exercised in prescribing ALEVE® NIGHTTIME during the first and second trimesters of pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause oligohydramnios, and renal dysfunction including renal failure (see* WARNINGS AND PRECAUTIONS*). ALEVE® NIGHTTIME is CONTRAINDICATED for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see* CONTRAINDICATIONS*).*

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- In self-medication, ALEVE® NIGHTTIME should only be used for a short-term treatment period of up to five days for pain associated with sleeplessness. Otherwise, a doctor should be consulted.
- Each dose should be swallowed with a full glass of water and can be taken fasting or with meals and/or antacids. Absorption may be slightly delayed with meals.
- If symptoms change, a doctor should be consulted.
- The recommended dosage should be adhered to unless directed by a doctor.

4.2 Recommended Dose and Dosage Adjustment

- **Adults and Children ≥ 12 years:** 2 caplets at bedtime. Do not take more than 2 caplets in a 24 hour period. Drink a full glass of water with each dose. The risk of heart attack or stroke may increase if you use more than the directed or for longer than directed.
- **Under 12 years:** Children under 12 should not take this drug. The safety in pediatric use has not been established.

4.4 Administration

See 4.2 Recommended Dose and Dosage Adjustment.

4.5 Missed Dose

Take once at night before bedtime. If you miss one night's dose, do not take twice the recommended dose on the next night.

5. OVERDOSAGE

Significant overdose can be characterized by drowsiness, heartburn, indigestion, nausea and vomiting. A few patients have experienced convulsions, but it is not clear if these were naproxen related. Some cases with acute, reversible renal failure have been described. It is not known what dose of the drug would be life-threatening.

Should a patient ingest a large quantity of naproxen sodium the stomach may be emptied and usual supportive measures like administration of activated charcoal employed. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. There is no specific antidote.

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet 220 mg Naproxen Sodium, 25 mg Diphenhydramine Hydrochloride	carnauba wax, FD&C Blue #2 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, talc, and titanium dioxide.

ALEVE® NIGHTTIME tablets are available in bottles in quantities of 20 and 40 caplets.

7. WARNINGS AND PRECAUTIONS

General

Patients who are taking any other analgesic or anti-inflammatory drugs (including naproxen or naproxen sodium), steroids, diuretics or drugs that influence hemostasis.

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

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.

Cardiovascular

Naproxen sodium: Patients with severe cardiac impairment and a history of hypertension. Naproxen sodium is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Naproxen may attenuate acetylsalicylic acid's antiplatelet effect. Patients should talk to their doctor if they are on an acetylsalicylic acid regimen and plan to take naproxen sodium (see the Drug-Drug Interactions section of the product monograph).

Cases of Kounis syndrome have been reported in patients treated with naproxen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Diphenhydramine: Vasconstrictive effects have been noted.

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.

Driving and Operating Machinery

See Neurologic.

Gastrointestinal

Patients with a medical history of gastrointestinal disease including peptic ulceration or gastrointestinal bleeding. Pain of gastrointestinal origin is not an indication for naproxen sodium.

Genitourinary

Diphenhydramine is not recommended to those with bladder neck obstruction.

Hematologic

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

Immune

Diphenhydramine: Hypersensitivity and anaphylaxis have occurred with diphenhydramine therapy.

Naproxen Sodium: Naproxen Sodium: Hypersensitivity reactions, including anaphylactic (anaphylactoid) reactions may occur both in patients with or without a history of hypersensitivity on exposure to naproxen-containing products, aspirin or other non-steroidal anti-inflammatory drugs

Cases of Kounis syndrome have been reported in patients treated with naproxen. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Monitoring and Laboratory Tests

Naproxen sodium causes transient, dose-dependent modestly increased bleeding times. However, these values often do not exceed the upper limit of the reference range. Naproxen sodium may theoretically interfere with the urinary analyses of 17-ketogenic steroids and 5-hydroxy indoleacetic acid (5 HIAA).

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

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs such as ALEVE®. If patients experience such adverse reactions, they should exercise caution in carrying out activities that require alertness, like driving or using machinery.

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 the Drug-Drug Interactions section).

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

Persons on a Low Sodium Diet

One caplet contains 20 mg sodium, which is classified as low in sodium. A variety of Health Canada guidelines suggest that a diet low in sodium should be restricted to 2 g per day while the Sodium Collaborative Research group suggests that a low-sodium diet should be restricted to ≤ 1.2 g (50 mmol) per day.

Psychiatric

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

Reproductive Health: Female and Male Potential

- **Fertility**

  Naproxen, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of naproxen should be considered.

Respiratory

Naproxen sodium: Patients with a medical history of asthma, rhinitis or nasal polyps.

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

Skin

Patients with a medical history of urticaria and angioedema.

Allergy Alert: Naproxen sodium may cause a severe allergic reaction, especially in people allergic to ASA. Symptoms may include: hives, facial swelling, asthma (wheezing), shock, skin reddening, rash and blisters. If an allergic reaction occurs, stop use and seek medical help right away.

7.1 Special Populations

7.1.1 Pregnant Women

Naproxen sodium: Caution should be exercised in prescribing ALEVE® NIGHTTIME during the first and second trimesters of pregnancy. As with other drugs of this type, naproxen sodium produces delay in parturition in animals and also affects the human fetal cardiovascular system

(closure of the ductus arteriosus). Therefore, naproxen sodium should not be used unless clearly needed and when directed to do so by a doctor. The use of naproxen sodium in the first and second trimesters of pregnancy requires cautious balancing of the possible benefits and risks to the mother and fetus, especially during the first trimester.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Oligohydramnios/Neonatal Renal Impairment:
Use of NSAIDs, including ALEVE® NIGHTTIME, at approximately 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some more severe cases, neonatal respiratory, musculoskeletal and renal problems (see TOXICOLOGY). Published studies and post-marketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment, or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required. If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary anywhere from the middle (onset approximately 20 weeks) to the end of the second trimester of pregnancy, it is recommended that the use be limited to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of fetal well-being, including of amniotic fluid volume assessment if ALEVE® NIGHTTIME treatment extends beyond 48 hours. It is recommended that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inform pregnant women not to use ALEVE® NIGHTTIME and other NSAIDs from the third trimester of pregnancy because of the risk of the premature closing of the fetal ductus arteriosus [see Contraindications]. If treatment with ALEVE® NIGHTTIME is needed for a pregnant woman anywhere from the middle (onset approximately 20 weeks gestation) to the

end of the second trimester of pregnancy, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours.

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.

7.1.2 Breast-feeding

Naproxen sodium: Naproxen has been found in the milk of lactating mothers. The use of naproxen sodium should therefore be avoided in women who are breast feeding unless clearly needed and directed to do so by a doctor.

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.

7.1.3 Pediatrics

Pediatrics (< 12 years of age)

Children under 12 should not take this drug, unless directed by a doctor. The safety in pediatric use has not been established.

7.1.4 Geriatrics

Patients older than 65 years and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. 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 esophageal injury including ulceration and bleeding.

The elderly are also more susceptible to the side effects of diphenhydramine. This drug may cause excitation rather than sedation in elderly patients.

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.

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety profile of ALEVE® NIGHTTIME was analyzed through clinical trials which were performed during the course of the ALEVE® NIGHTTIME clinical development program. The clinical development program included a total of 3 randomized, double-blind studies and used ALEVE® NIGHTTIME in single or multiple doses. In total 678 subjects were treated with ALEVE® NIGHTTIME while 257 took ALEVE® and 109 took placebo. Seventy-two percent of subjects

participated in single dose trials and 28% participated in multi-dose trials lasting for 10 days. The adverse events most commonly reported (>1%) were related to the gastrointestinal (nausea 4.42%, vomiting 1.03%) and nervous system (dizziness 2.51%, headache 2.21%). There were no serious gastrointestinal adverse events (bleeding or perforation) or any case of anaphylaxis.

In post-market adverse reactions observed for OTC naproxen sodium and/or prescription dosages (higher dose and/or longer duration), the most commonly (≥ 1% - < 10%) observed adverse events are gastrointestinal in nature or associated with the nervous system. The most common adverse drug reactions for OTC naproxen sodium are dizziness, headache, light-headedness, dyspepsia, nausea, heartburn, and abdominal pain. The adverse drug reactions seen during short term use of naproxen sodium are normally mild and disappear after discontinuing the drug. In short term use of naproxen sodium occurrence of GI ulcers/bleeding/perforation are rare events. The adverse events are related to NSAIDs as a class; there is no adverse event that is specific for naproxen alone.

8.2 Clinical Trial Adverse Reactions

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

The safety profile of ALEVE® NIGHTTIME was analyzed through clinical trials which were performed during the course of the ALEVE® NIGHTTIME clinical development program. The clinical development program included a total of 3 studies, which satisfied the criteria of being randomize and double-blind and used ALEVE® NIGHTTIME in single or multiple doses. In total 678 subjects were treated with ALEVE® NIGHTTIME while 257 took ALEVE® and 109 took placebo. Seventy-two percent of subjects participated in single dose trials and 28% participated in multi-dose trials lasting for 10 days. Subjects were predominantly Caucasian and included slightly more women. Most subjects were in their 20s to 30s with the exception of 176 patients in the placebo-controlled study who were over the age of 60. The data in table 1 shows the frequencies of adverse events that are >1%. There were no serious gastrointestinal adverse events (bleeding or perforation) or any case of anaphylaxis.

Table 2 - Adverse events that occurred with ALEVE® NIGHTTIME with a frequency > 1% in clinical trials.

	ALEVE® NIGHTTIME N = 785 (%)	ALEVE N = 363 (%)	DPH N = 183 (%)	Placebo N = 109 (%)
Gastrointestinal				
Nausea	30 (4.42%)	15 (5.84%)	12 (9.30%)	0 (0.0%)
Vomiting	7 (1.03%)	6 (2.33%)	6 (4.65%)	0 (0.0%)
Nervous System				
Dizziness	17 (2.51%)	6 (2.33%)	4 (3.10%)	0 (0.0%)
Headache	15 (2.21%)	16 (6.23%)	9 (6.98%)	0 (0.0%)

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Cardiac
- Tachycardia

Eye Disorders
- Eye swelling
- Vision blurred

General Disorders
- Feeling Hot
- Pyrexia
- Chills

Immune System Disorders
- Hypersensitivity
- Seasonal allergy

Infections and Infestations
- Nasopharyngitis
- Urinary tract infection
- Pharyngitis streptococcal
- Rhinitis
- Upper respiratory tract infection

Injury, Poisoning and Procedural Complications
- Contusion
- Excoriation
- Laceration
- Muscle strain

Metabolism and Nutrition Disorders
- Hyperglycemia
- Decreased appetite
- Gout
- Hyperkalemia

Nervous System
- Presyncope
- Syncope
- Paraesthesia

Psychiatric Disorders
- Insomnia
- Restlessness
- Anxiety
- Depression

Renal and Urinary Disorders
- Glycosuria
- Haematuria

Reproductive System and Breast Disorders
- Dysmenorrhoea

Respiratory, Thoracic, Mediastinal
- Pharyngolaryngeal pain
- Epistaxis
- Alveolitis
- Nasal congestion
- Sinus congestion
- Hiccups
- Oropharyngeal pain
- Sneezing
- Dry throat
- Rhinorrhea

Skin and Subcutaneous Tissue
- Pruritis
- Hyperhidrosis
- Rash generalized

Vascular
- Hypertension
- Flushing

8.5 Post-Market Adverse Reactions

Post-Market Adverse Drug Reactions for Naproxen Sodium

Table 3 - The following post-marketing adverse drug reactions have been observed for OTC naproxen sodium and/or solely for prescription dosages (higher dose and/or longer duration) of naproxen/naproxen sodium.

Immune system	Very rare < 0.01% and isolated reports	Anaphylaxis/anaphylactoid reactions
	Not Known (cannot be estimated from the available data)	Kounis syndrome (see section 7 WARNINGS AND PRECAUTIONS)
Blood	Very rare < 0.01% and isolated reports	hematopoietic disturbances (leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia, eosinophilia, hemolytic anemia)
Psychiatric	Very rare < 0.01% and isolated reports	psychiatric disorders
Nervous	Common ≥ 1% - < 10%	dizziness, headache, lightheadedness
	Uncommon ≥ 0.1 % - < 1 %	drowsiness, insomnia, somnolence
	Very rare < 0.01% and isolated reports	aseptic meningitis, cognitive dysfunction, convulsions
Eye	Very rare < 0.01% and isolated reports	visual disturbance, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema

Ear& labyrinth	Uncommon ≥ 0.1 % - < 1 %	vertigo
	Very rare < 0.01% and isolated reports	hearing impairment, tinnitus
Cardiac	Very rare < 0.01% and isolated reports	congestive heart failure, hypertension, pulmonary edema
Vascular	Very rare < 0.01% and isolated reports	vasculitis
Respiratory	Very rare < 0.01% and isolated reports	dyspnea, asthma, eosinophilic pneumonitis
Gastrointestinal	Common ≥ 1% - < 10%	dyspepsia, nausea, heartburn, abdominal pain
	Uncommon ≥ 0.1 % - < 1 %	diarrhea, constipation, vomiting
	Rare ≥ 0.01% - < 0.1%	peptic ulcers without or with bleeding or perforation, gastrointestinal bleeding, hematemesis, melena
	Very rare < 0.01% and isolated reports	pancreatitis, colitis, aphthous ulcers, stomatitis, esophagitis, intestinal ulcerations
Hepatobiliary	Very rare < 0.01% and isolated reports	hepatitis, icterus
Skin & subcutaneous tissue	Uncommon ≥ 0.1 % - < 1 %	exanthema (rash), pruritus, urticaria
	Rare ≥ 0.01% - < 0.1%	angioneurotic edema
	Very rare < 0.01% and isolated reports	alopecia (usually reversible), photosensitivity, porphyria, exudative erythema multiforme, epidermal necrolysis, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, Systemic Lupus Erythematosus, Stevens-Johnson syndrome, photosensitivity reactions including porphyria cutanea tarda ("pseudoporphyria") or epidermolysis bullosa

Renal & urinary	Rare ≥ 0.01% - < 0.1%	renal impairment
	Very rare < 0.01% and isolated reports	interstitial nephritis, renal papillary necrosis, nephrotic syndrome, renal failure, renal disease
Pregnancy	Very rare < 0.01% and isolated reports	Induction of labour
Congenital	Very rare < 0.01% and isolated reports	Closure of ductus arteriosus, orofacial clefts as an isolated report
Reproductive	Very rare < 0.01% and isolated reports	female infertility
General disorders	Rare ≥ 0.01% - < 0.1%	peripheral edema, particular in patients with hypertension or kidney failure, pyrexia
Investigations	Very rare < 0.01% and isolated reports	raised serum creatinine, abnormal liver function test

Severe allergic ADRs are very rare events, which are more likely to occur in subjects who have experienced allergic reactions previously. In short term use of naproxen sodium occurrence of GI ulcers/bleeding/perforation are rare events.

The adverse drug reactions seen during short term use of naproxen sodium are normally mild and disappear after discontinuing the drug. The most common ADRs for OTC naproxen sodium and/or solely for prescription doses (higher dose and or longer duration) are dizziness, headache, light-headedness, dyspepsia, nausea, heartburn, and abdominal pain. Uncommonly drowsiness, insomnia, and skin rashes are encountered. Peripheral edemas are rare events. Other ADRs are very rare and/or observed through isolated reports only. The adverse events are common to all NSAIDs as a class; there is no adverse event that is specific for naproxen alone.

9. DRUG INTERACTIONS

9.2 Drug Interactions Overview

Naproxen Sodium and Diphenhydramine Hydrochloride

Alcohol and Other CNS Depressant Drugs

Because of the possibility of additive CNS depressant effects, patients should avoid alcoholic beverages when taking ALEVE® NIGHTTIME. (See Warnings and Precautions, Neurologic).

Antidepressants such as amitriptyline, amoxapine, belladonna alkaloids, clomipramine, procarbazine and triflupromazine may increase the possibility of dry mouth, urinary retention, adynamic ileus, chronic glaucoma and altered mental status. Caution is necessary if ALEVE® NIGHTTIME is taken with other antihistamines, tranquilizers or any other sedating drug (encompassing any other diphenhydramine product including topical applications) or with prescription drugs used to treat depression.

Naproxen Sodium

During short term use of naproxen sodium, interactions with the following medications could be of clinical significance.

9.4 Drug-Drug Interactions

The drugs listed in table 4 are based on either drug interaction case reports or studies.

Table 4 - Established or Potential Drug-Drug Interactions

Proper Name	Effect	Clinical comment
Cyclosporine	cyclosporin concentrations may increase, which could induce nephrotoxicity	These patients should be monitored adequately.
Lithium	in some patients, lithium concentrations may increase, which could induce nausea, polydipsia, polyuria, tremor, confusion	These patients should be monitored adequately
Methotrexate	if weekly methotrexate intake exceeds 15 mg, methotrexate concentrations may increase which could induce blood dyscrasia, nephrotoxicity, mucosal ulcerations	These patients should be monitored adequately
NSAIDs	adds to the risk of gastro-intestinal bleeding	Should be avoided; however, effects may be minimised by using the lowest effective dose for the shortest duration necessary.
Low dose ASA (81mg to 325mg daily, for cardiovascular protection e.g. ASPIRIN® 81mg)	Can add to the risk of gastro-intestinal bleeding and may attenuate the irreversible platelet inhibition induced by acetylsalicylic acid	These patients should be monitored adequately
Anticoagulants	adds to the risk of gastro-intestinal bleeding	These patients should be monitored adequately

Proper Name	Effect	Clinical comment
Glucocorticoids	adds to the risk of gastro-intestinal bleeding	These patients should be monitored adequately
Diuretics, antihypertensive drugs including ACE Inhibitors, β blockers	the diuretic and antihypertensive efficacy, particular in patients with pre-existing nephropathy, may be reduced	These patients should be monitored adequately. Concomitant use with diuretics may increase risk of congestive heart failure.

In a 2005 American case-control study, labelled, short term use of OTC naproxen or OTC ibuprofen was not associated with GI risk nor was there any detectable interaction with ASA at this dose level; furthermore, there was no difference between OTC naproxen or OTC ibuprofen. An increased risk could be attributed with concomitant use of ASA and high dose NSAIDs; however, the numbers of exposed cases were small.

Another American retrospective database study found an odds ratio of 2.07 (1.23 – 3.49) for GI complications with concomitant use of low dose ASA and OTC-dose naproxen; for comparison, this ratio was 3.36 (2.36 – 4.80) in subjects taking OTC-dose ibuprofen and low dose ASA; the corresponding ratio for naproxen as monotherapy was 1.54 (1.04-2.28) which is not significantly different from the combined therapy. The corresponding ratio for ibuprofen as monotherapy was 1.38 (1.07-1.78) which is significantly lower than the combined therapy of ibuprofen and low dose ASA therapy.

Due to the nature of the study, information regarding the duration of naproxen and ibuprofen intake could not be collected. The findings are consistent with previous study results indicating increased GI risk in patients taking OTC-NSAIDS for longer terms or prescription NSAIDs while on low dose ASA.

Labelled, short term use of OTC naproxen together with low dose ASA was not associated with a detectable GI-risk; longer term use (mainly >10 days) of NSAIDs in OTC doses and concomitant ASA can increase the relative risk a little, adding however only very little absolute risk.

Naproxen may attenuate the irreversible platelet inhibition induced by acetylsalicylic acid. Clinical pharmacodynamic data suggest that concurrent (same day) naproxen sodium/ naproxen usage for more than one day consecutively inhibits the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen sodium/ naproxen therapy. The clinical relevance of this interaction is not known. Treatment with naproxen / naproxen sodium in patients with increased

cardiovascular risk may limit the cardiovascular protection of acetylsalicylic acid.

During short term use of naproxen sodium interactions of clinical significance do not seem to be relevant for the following medications: antacids, antidiabetics, hydantoins, probenecid, zidovudine.

9.5 Drug-Food Interactions

Tablets: The absorption may be slightly delayed with a meal

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established

9.7 Drug-Laboratory Test Interactions

Naproxen sodium causes transient, dose-dependent modestly increased bleeding times. However, these values often do not exceed the upper limit of the reference range. Naproxen sodium may theoretically interfere with the urinary analyses of 17-ketogenic steroids and 5-hydroxy indoleacetic acid (5 HIAA).

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Naproxen Sodium

Naproxen like all other nonsteroidal anti-inflammatory drugs (NSAIDs) is an analgesic, antipyretic and anti-inflammatory medication. ALEVE works at both the site of pain and centrally. The principal mechanism of action relies on the inhibition of prostaglandin synthesis. Prostaglandins are naturally occurring fatty acids derivates that are widely distributed in the tissues, and are involved in the production of pain, fever and inflammation. NSAIDs inhibit prostaglandin synthesis through inhibition of the cyclo-oxygenase enzymes. The anti-inflammatory and analgesic activity of these drugs is based on the concept that prostaglandins sensitize the tissues to pain- and inflammation-producing mediators and the antipyretic activity is assumed to be due to inhibition of prostaglandin synthesis in the hypothalamus induced by infectious states such as the common cold.

Diphenhydramine Hydrochloride

Diphenhydramine is a first generation H1 receptor antagonist of the ethanolamine class that is available over-the counter for use as a sedative, hypnotic, antihistamine, antitussive, and antiemetic agent.

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.

10.2 Pharmacodynamics

In low dose, that is ≤ 660 mg naproxen sodium daily, the analgesic and anti-pyretic activities prevail, while higher doses mostly are necessary for a full anti-inflammatory activity response. Significant naproxen plasma levels and onset of pain relief can be obtained within 20 minutes of intake.

10.3 Pharmacokinetics

Absorption

Naproxen sodium

Naproxen sodium promptly dissolves in the gastric juice to sodium and fine particles of naproxen. Naproxen is rapidly and completely absorbed from the gastrointestinal tract. The peak plasma level (Cmax) of 53-66 g/ml is reached approximately 1-1½ hours after intake of 440mg naproxen sodium. For ALEVE Caplets, food can slightly delay naproxen absorption but not the extent, and for ALEVE Liquid Gels, food delays naproxen absorption. The kinetics are dose linear up to 550 mg naproxen sodium twice daily. Plasma concentrations of un-bound circulating naproxen, the active component, of about 10 ng/ml exert analgesic action and correspond to a total naproxen plasma concentration of 15 μg/ml.

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.

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.

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.

Distribution:

Naproxen Sodium

The volume of distribution of naproxen is small, about 0.1 l/kg. Steady-state concentrations are obtained in two days, and no significant accumulation has been observed. More than 99% of the circulating naproxen is albumin-bound.

Diphenhydramine Hydrochloride

The distribution of diphenhydramine into human body tissues and fluid has not been fully characterized. Following intravenous (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. The volume of distribution of the drug reportedly is larger in Asian (about 480 L) than in Caucasian adults. The drug crosses the placenta and has been detected in milk, although the extent of distribution in milk has not been quantified.

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.

Metabolism:

Naproxen Sodium

Naproxen is either metabolised (cytochrome P450) to 6-0-desmethyl naproxen (6-DMN) and conjugated to glucuronides or left un-metabolised. Naproxen does not induce metabolizing enzymes.

Diphenhydramine Hydrochloride

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

Elimination:

Naproxen Sodium

Naproxen and its metabolites are primarily excreted via the kidneys (>95%). The elimination half-life of naproxen is about 14 hours. The rate of excretion has been found to coincide closely with the rate of drug disappearance from plasma.

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.

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.

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.

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.

Special Populations and Conditions

- **Geriatrics** There is no evidence of differential metabolism or excretion in the elderly.
- **Sex** There is no evidence of differential metabolism or excretion between genders.
- **Hepatic Insufficiency** In case of severe hepatic insufficiency circulating albumin is decreased giving rise to increased fractions of free and unbound naproxen.
- **Renal Insufficiency** In case of severe renal insufficiency protein binding is lower giving rise to increased fractions of free and unbound naproxen. In patients with severely reduced glomerular filtration, the rate of urinary excretion may be reduced. Naproxen, in contrast to its non-active metabolite 6-DMN, is not cleared from the body during haemodialysis.

11. STORAGE, STABILITY AND DISPOSAL

Store between 15 - 30°C.

12. SPECIAL HANDLING INSTRUCTIONS

No special handling instructions.

PART II: SCIENTIFIC INFORMATION

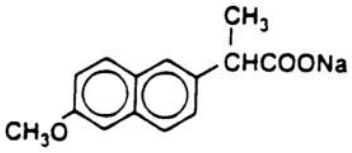
13. PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Naproxen sodium

Chemical name: 2-Napthaleneacetic acid, 6-methoxy –α -methyl-, sodium salt, (-).

Molecular formula and molecular mass: C14H13NaO3, 252.24

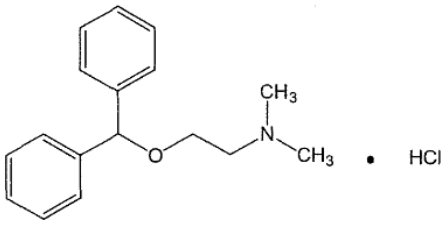
Structural formula: 

Physicochemical properties: Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water with a melting point of about 255°C with decomposition.

Proper name: Diphenhydramine hydrochloride

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

Molecular formula and molecular mass: C17H21NO.HCl; 291.82

Structural formula: 

Physicochemical properties: Diphenhydramine Hydrochloride is a white, odourless, crystalline powder. Freely soluble in water, in alcohol, and in chloroform; sparingly soluble in acetone; very slightly soluble in benzene and in ether. The melting point is 167º-172ºC.

14. CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Studies with Naproxen Sodium

The published trials regarding the efficacy of ALEVE consist of 4 studies; three dental extraction trials and 1 trial evaluating the efficacy for short term treatment of knee osteoarthritis. These studies have documented the efficacy of 220mg and 440mg doses of naproxen sodium in treating various pain states extrapolated from the dental pain model, as well as the treatment of arthritis pain.

Studies with Diphenhydramine Hydrochloride (DPH)

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

Studies with Naproxen Sodium and Diphenhydramine Hydrochloride

The clinical trials to support the efficacy of ALEVE® NIGHTTIME consist of 1 multicenter, randomized, double-blind, parallel-group study designed to assess the efficacy of a single oral dose of ALEVE® NIGHTTIME in subjects with post-surgical dental pain and phase-advanced sleep.

Study demographics and trial design

Healthy male and female volunteers, age 12 years and older, who were scheduled to undergo surgical removal of at least 2 third molars, 1 of which had to be a mandibular third molar, were eligible to participate in this study. Patients also had to report moderate to severe postoperative pain on a 4-point Categorical Pain Rating Scale and score >50mm on the 100-mm visual analog Pain Severity Rating Scale. Subjects were housed and observed at the Clinical Research Unit overnight and required to go to bed approximately 5 hours earlier than usual. A single dose of ALEVE® NIGHTTIME was administered and evaluated for efficacy. All subjects were in good general health, of both sexes and any race, and were between the ages of 16-48.

14.2 Study Results

Table 5 - Summary of Patient Demographics for Pivotal Clinical Trial

Study Ref. Indication	Trial design & Indication	Duration	Dose (mg) ALEVE® NIGHTTIME & Comparators	Study subjects	Mean age (SD)	Gender M/F
Buchanan 14837	MC, R, DB, SD Extraction of 2-4 molars	10 hours	ALEVE® NIGHTTIME 440mg/50mg (2 x 220mg / 25mg) ALEVE 440mg (2 x 220mg) DPH 50mg (2 x 25mg)	508 healthy subjects	21.3 (4.99)	229/279

Table 6 - Overview of Pivotal Clinical Trial Result

Study	Endpoints	Associated values and statistical significance for ALEVE® NIGHTTIME (A), ALEVE (B) and DPH (C)				
		ALEVE® NIGHTTIME	ALEVE	DPH	A vs. B	A vs. C
Buchanan 14837	Wake After Sleep Onset (mean)	142.2	214.3	429.5	0.0002	< 0.0001
	Sleep Latency (median)	25.50	25.75	41.50	NS	< 0.0001
	Total Sleep Time (mean)	427.7	355.6	143.2	0.0001	-----
	Sleep Efficiency (mean)	71.3	59.3	23.9	0.0007	-----
	Sleep Quality (mean)[1]	2.1	1.4	1.7	< 0.0001	0.0494
	Pain Intensity[2] (LS-mean)	-1.2	-0.9	0.1	0.0064	< 0.0001
	Pain Relief[3] (mean)	2.4	2.0	0.6	0.0047	< 0.0001
	Subjective Assessment of Pain Relief[4] (mean)	2.9	2.8	1.8	0.2734	< 0.0001
	Proportion Taking Rescue Medication (%)	18.7	27.1	49.0	0.0053	< 0.0001

The dental pain model, i.e., tooth extraction model, is accepted as the model of choice to establish analgesic efficacy. Results from this model can be extrapolated to other pain states that are relevant for OTC medication. The phase advanced sleep model causes disruption in a variety of sleep parameters, having the greatest impact on sleep maintenance parameters. As a result, the phase advanced sleep model has been shown to be a useful model to study the effects of drugs on transient insomnia. The pivotal efficacy study demonstrates that ALEVE® NIGHTTIME provides fast and effective pain relief and relieves occasional sleeplessness associated with minor aches and pain.

The safety data for ALEVE® NIGHTTIME is derived from single-dose and multiple-dose clinical trials. In the clinical trials for ALEVE® NIGHTTIME, the most common adverse reactions were nausea, headache, dizziness and vomiting, occurring in a small percentage of subjects, with no difference between ALEVE® NIGHTTIME, ALEVE, or DPH. Serious adverse reactions, like gastrointestinal bleeding or anaphylactic shock did not occur in any subject enrolled in the clinical trials. There were no deaths and no serious AEs. No subject was discontinued due to an AE.

Overall, ALEVE® NIGHTTIME is an effective analgesic plus sleep-aid suitable for the relief of occasional sleeplessness associated with minor aches and pain.

[1] Sleep quality was assessed via Global Assessment of the Investigational Product as a Sleep Aid, where 0 = poor and 4 = excellent.
[2] Pain intensity was collected on a 4-point Categorical Pain Rating Scale, where 0 = no pain and 3 = severe pain. A negative value represents a reduction in pain intensity.
[3] Overall rating of pain relief was assessed using a 0 to 4 scale, where 0 = no relief and 4 = complete relief.
[4] Subjective assessment of ALEVE Nightime as a pain relieve was assess via Global Assessment of the Investigational Product as a Sleep Aid, where 0 = poor and 4 = excellent.

14.3 Comparative Bioavailability Studies

A single dose, 4-way pharmacokinetic study of 2 x ALEVE® NIGHTTIME (220 mg naproxen sodium / 25mg DPH), 2 x ALEVE tablets (220 mg naproxen sodium) and 2 x Allergy Relief® tablets (DPH 25mg) was conducted in 32 healthy volunteers (15 male; 17 female) under fasting conditions. A summary of the comparative bioavailability data is presented below:

Naproxen (2 x 220mg naproxen sodium) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**ALEVE® NIGHTTIME**	**ALEVE**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (µg.hr/mL)	903.4 913.2 (14.87)	900.7 909.1 (13.73)	100.30	98.7, 102.0
AUC_I (µg.hr/mL)	1053 1063 (14.76)	1052 1060 (13.87)	100.10	99.8, 105.2
C_{max} (µg/mL)	73.92 74.64 (13.89)	79.53 80.41 (14.29)	92.95	87.9, 98.3
T_{max} (median) (h)	1.25 [0.33-3.00]	0.75 [0.50-3.00]		
$T_{½}$ (h)	17.02 (3.823)	16.52 (2.563)		

Diphenhydramine (2 x 25mg DPH) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**ALEVE® NIGHTTIME**	**DPH**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (µg.hr/mL)	570.6 613.9 (38.84)	556.8 598.2 (39.03)	102.47	97.6, 107.1
AUC_I (µg.hr/mL)	602.4 646.5 (37.06)	589.7 636.4 (40.47)	102.15	97.1, 107.1
C_{max} (µg/mL)	62.88 67.72 (40.06)	65.43 68.86 (32.60)	96.10	86.8, 106.4
T_{max} (median) (h)	2.5 [1.00-4.02]	1.75 [1.00-3.00]		
$T_{½}$ (h)	10.96 (2.685)	10.85 (2.474)		

This single dose, 4-way pharmacokinetic study of 2 x ALEVE® NIGHTTIME (220mg naproxen sodium / 25mg DPH), 2 x ALEVE tablets (220mg naproxen sodium) and 2 x Allergy Relief tablets (25mg DPH) was also conducted in 32 healthy volunteers (15 male; 17 female) under fed conditions. Results show that the Cmax of naproxen is reduced under fed conditions (i.e., 90% confidence interval is not within 80.0% to 125.0%); there is no effect on AUC. A summary of the comparative bioavailability data of ALEVE® NIGHTTIME under fasting versus fed conditions is presented below:

Naproxen (2 x 220mg naproxen sodium) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**ALEVE® NIGHTTIME (fasting)**	**ALEVE® NIGHTTIME (fed)**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (µg.hr/mL)	903.4 913.2 (14.87)	874.2 882.4 (13.51)	96.77	95.2, 98.4
AUC_I (µg.hr/mL)	1053 1063 (14.76)	971.5 980.7 (14.15)	92.26	92.1, 97.0
C_{max} (µg/mL)	73.92 74.64 (13.89)	59.80 60.83 (18.30)	80.90	76.1, 85.1
T_{max} (median) (h)	1.25 [0.33-3.00]	3.00 [0.75-6.00]		
$T_{½}$ (h)	17.02 (3.828)	16.39 (2.563)		

Naproxen (2 x 220mg naproxen sodium) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**ALEVE® NIGHTTIME (fasting)**	**ALEVE® NIGHTTIME (fed)**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
Diphenhydramine (2 x 25mg DPH) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**ALEVE® NIGHTTIME (fasting)**	**ALEVE® NIGHTTIME (fed)**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (µg.hr/mL)	570.6 613.9 (38.84)	639.6 685.3 (38.46)	112.09	107.6, 118.1
AUC_I (µg.hr/mL)	602.4 646.5 (37.06)	664.7 709.5 (37.64)	110.34	108.2, 119.6
C_{max} (µg/mL)	62.88 67.72 (40.06)	70.77 77.07 (45.39)	112.55	102.2, 125.4
T_{max} (median) (h)	2.5 [1.00-4.02]	2.5 [1.25-6.00]		
$T_{½}$ (h)	10.96 (2.685)	10.80 (1.883)		

15. MICROBIOLOGY

No microbiological information is required for this drug product.

16. NON-CLINICAL TOXICOLOGY

Naproxen Sodium

The oral LD_{50} of naproxen sodium is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs. No carcinogenic or embryotoxic properties were detected and since the launch of naproxen in the beginning of the 1970's no experience or information has been obtained that could indicate such properties.

Subacute and Chronic Oral Studies

In subacute and chronic oral studies with naproxen in a variety of species, the principle pathologic effect was gastrointestinal irritation and ulceration. The lesions seen were predominantly in the small intestine and ranged from hyperaemia to perforation and peritonitis. Similar results have been reported with other non-steroidal anti-inflammatory agents such as ibuprofen, phenylbutazone, ASA, indomethacin and mefenamic acid.

Nephropathy was seen occasionally in acute and subacute studies in rats, mice and rabbits at high-dose levels of naproxen, but not in rhesus monkeys, miniature pigs or dogs. In the affected species the pathologic changes occurred in the cortex and papilla. Some rats examined 14 days after single oral doses of 230 mg/kg or more of naproxen evidenced necrotic areas of cortical and papillary tissue. Tubular dilation (ectasia) occurred in rabbits dosed orally for 14 days with 200mg/kg/day or more of naproxen. An examination of unfixed renal tissue from rabbits so treated was conducted and revealed the presence of diffraction patterns similar to that of crystalline naproxen. This suggests that the ectasia observed was a physical response to deposition of excreted naproxen within the tubules.

In mice given oral doses of 120 mg/kg/day or more of naproxen for 6 months, the kidneys were characterized by a low but non-dosage-related incidence of cortical sclerosis and papillary tip necrosis. Chronic administration of high doses of naproxen to mice appears to be associated with exacerbation of spontaneous murine nephropathy.

Rhesus monkeys were administered daily doses of 7, 20, or 60 mg/kg and the monkeys received these daily doses for the next six months. No evidence of drug-related pathology was seen in this study. In a 1 year study in rhesus monkeys at daily doses of 100, 140, 180 mg/kg renal lesions consistent with those described for analgesic nephropathy were observed. The severity of the lesions was generally dose related.

A similar catalogue of renal responses has been reported in the laboratory animals treated with a variety of non-steroidal anti-inflammatory agents.

A wide range of susceptibility to gastrointestinal lesions from administration of naproxen was evident in the various species tested. For example, 30mg/kg/day was tolerated well by rats for 90 days, but the same dose was ulcerogenic when administered for 6 months. Rhesus monkeys and miniature swine exhibited no significant pathology when dosed with naproxen at 45 mg/kg/day for 30 days. This dose of naproxen was also tolerated by miniature swine without obvious evidence of adverse effects when administered daily for 1 year. In rhesus monkeys, doses as high as 120 mg/kg/day (60 mg/kg b.i.d.) for 6 months produced no clinical or histopathological evidence of gastrointestinal irritation although occult blood in the feces occurred more frequently in these animals compared to controls. Daily administration of naproxen to rhesus monkeys for one year was associated with mild gastric irritation in a few animals receiving 100, 140 or 180 mg/kg. In rabbits the maximum tolerated repeated oral dose is 80 to 100 mg/kg/day. Mice survived oral daily doses of 240 mg/kg/day for 6 months. In dogs, on the other hand, 5.0 mg/kg/day approaches the maximum tolerated dose. This peculiar canine

susceptibility to gastrointestinal effects of non-steroidal anti-inflammatory agents has also been shown with indomethacin and ibuprofen.

In dogs naproxen exhibits a considerably longer plasma half-life than it does in rats, guinea pigs; miniature swine, monkeys, and man. The same observation has been made with ibuprofen in dogs compared to rats and man. In addition, in the species listed, only the dog excretes significant amounts of administered naproxen in the feces (50%). In the rat, guinea pigs, miniature swine, monkey and man, 86-90% of the administered drug is excreted in the urine. The suggested enterohepatic circulation of naproxen in the dog (as judged by fecal excretion) most likely is a major factor in the susceptibility of the dog to gastrointestinal irritation by this compound.

In subacute and chronic toxicity studies, other pathological changes were often seen which were considered to be clearly secondary to the effects of naproxen on the gastrointestinal tract. These consisted of peritoneal inflammation and adhesions, mesenteric lymphadenopathy, decreased haemoglobin and hematocrit levels, leucocytosis, evidence of stimulated hematopoeisis and elevated plasma glutamic oxaloacetic transaminase.

As noted above, gastrointestinal pathology in laboratory animals is a finding common to non-steroidal anti-inflammatory agents.

Ophthalmic examinations were made in the two-year rat study and the one year monkey study. No eye changes considered to be drug related were noted except for the observation of pale irides in the rats. This was secondary to anemia as a result of gastrointestinal blood loss and did not represent a toxic effect of naproxen on the eye.

Plasma levels of naproxen were measured in monkeys dosed for one year with 100, 140 or 180 mg/kg/day naproxen. Plasma levels after 1 week of dosing were not significantly different from those after 12 months of dosing. As judged by these results there was no evidence of tachyphylaxis or accumulation over the 1-year dosing period.

Moderate weight loss of the male secondary sex glands occurred in some studies in naproxen-treated rats and dogs. Histopathologically, the affected glands in some instances exhibited atrophic and/or hypoplastic changes characterized by decreased secretory material. A possible estrogenic action of naproxen as a causative factor seems highly unlikely since in standard bioassay procedures the drug exhibited no estrogenic activity.

Daily doses of naproxen as high as 30 mg/kg administered for 60 days before mating had no effect on fertility and reproductive performance of male rats. These results reflect the physiological integrity of the entire male reproductive apparatus after administration of naproxen throughout the spermatogenic cycle.

Diphenhydramine Hydrochloride

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

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.

Carcinogenicity: To evaluate the carcinogenic potential of naproxen, the compound was administered in the feed to rats for up to 2 years. Naproxen did not reveal any carcinogenic potential in rats.

Mutagenicity: Mutagenicity tests were performed with naproxen using 5 strains of bacteria and one of yeast. The test was carried out with and without mammalian microsomal activation. Naproxen was also tested in the mouse lymphoma assay. Naproxen was not mutagenic.

Reproductive and Developmental Toxicology: Daily oral administration of 15, 30 or 60 mg/kg of naproxen to female rabbits from 2 weeks before mating until day 20 of pregnancy did not affect fertility, gestation, or the numbers of live fetuses.

In a peri- and post-natal study in rats, oral doses of naproxen up to 20 mg/kg administered daily during the last part of pregnancy through weaning did not result in adverse effects in viability of pups, lactation index, sex ratio or weight gain of offspring. However, there was a slight increase in gestation length at the 10 and 20 mg/kg dose levels; and, at the 10 mg/kg dose level, there was a significant increase in stillbirths.

The mechanism of this phenomenon in the rats is not entirely clear at present. It is possible that difficulties in delivery in naproxen-treated rats reflect a general underlying maternal debility induced by increased susceptibility of the pregnant animals to gastrointestinal ulceration and subsequent peritonitis. Such an observation has been reported with ibuprofen. Pregnant animals were reported to be 9 times more susceptible to the ulcerogenic effects of that compound than were non-pregnant animals. Similarly, with naproxen, gastrointestinal lesions in non-pregnant paired drug-treated controls were found to occur less frequently and were less extensive than those in pregnant rates treated daily from day 15 of pregnancy through term.

More recent evidence, however, suggests that inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory compounds may be related to decreased uterine contractility. Thus, the onset of labour in a rat model system can be delayed with naproxen administration without causing maternal or fetal deaths in excess of that seen in controls. Since it has been shown that naproxen inhibits prostaglandin synthesis in vitro, it has been suggested that the effects of naproxen on uterine contractility are mediated through that mechanism.

Maternal and fetal deaths seen in naproxen-treated rats were, therefore, apparently related to dystocia rather than to a direct toxic effect of the compound. Naproxen is not unique in this regard since comparable results were obtained in the rat with other commonly used non-

steroidal anti-inflammatory agents (ASA, indomethacin, mefenamic acid and phenylbutazone). Similar results have been suggested in reports of other animal studies with ibuprofen.

In a fertility and reproduction study in mice, the dams were dosed daily with 12, 36 or 108 mg/kg from 14 days prior to mating through weaning. At the highest dose level, there was an increase in maternal deaths which was reflected in decreased 21-day survival and lactation indices. There were no other changes in the parameters examined. In a similar study in rats, daily doses were 2, 10 or 20 mg/kg from 14 days before mating through weaning. Other than decreased survival to weaning which appeared due to poor maternal care in pups born to high dose dams, there were no differences between control and treated groups. One mid and one high dose dam died during labour due to delayed parturition.

The toxicity of naproxen in juvenile animals was compared to that in adult animals. The results of single oral dose LD50 studies in weanling rats and mice, run simultaneously with studies in adult animals, revealed no significant differences in the values obtained with mature and immature animals of both species.

An additional study with juvenile mice consisted of two parts. Weaning animals were treated daily for one month with a pediatric formulation of naproxen. At the end of the treatment period a portion of the animals were examined for pathologic changes. The remaining animals were allowed to reach maturity and breed.

The usual gastroenteropathy characteristic for non-steroidal anti-inflammatory agents was observed in some high dose (135 mg/kg) mice. Naproxen administration for the first post-weaning month of life did not compromise in any way the later fertility or reproductive capacity of mice so treated.

Teratology: In embryotoxicity studies no skeletal or visceral anomalies or pathologic changes were induced in the fetuses of pregnant rats and rabbits treated during organogenesis with daily oral doses of naproxen up to 20 mg/kg nor in mice similarly treated with 30 or 50 mg/kg. In these studies, there were also no significant differences from controls in the number of live fetuses, resorptions, fetal weights or ano-genital distances. In another mouse study no malformations were observed with administration of 60 or 120 mg/kg of naproxen although there was a slight reduction in numbers of live fetuses in both dose groups and in fetal body weight in the high dose group.

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ALEVE® NIGHTTIME
Naproxen Sodium 220 mg and Diphenhydramine Hydrochloride 25 mg Tablets

Read this carefully before you start taking **ALEVE® NIGHTTIME**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ALEVE® NIGHTTIME**.

Serious Warnings and Precautions
Risk in Pregnancy: Talk to your doctor if you are trying to conceive, in your first or second trimester of pregnancy or if breastfeeding.

What is ALEVE® NIGHTTIME used for?
- Trust ALEVE® NIGHTTIME for providing fast and effective relief of occasional, night time, minor pain and accompanying sleeplessness due to aches and pain associated with joints, muscles, backache, headaches, toothaches, as well as pain of migraine, dental extractions, inflammation and arthritis.
- Helps you to fall asleep and stay asleep.
- For use only if you have short-term night time sleeplessness caused by pain. If this is not the case, do not use.

How does ALEVE® NIGHTTIME work?
ALEVE® NIGHTTIME is a pain reliever and sleep aid. The pain relief from naproxen sodium helps to fall asleep and diphenhydramine hydrochloride helps to stay asleep.

What are the ingredients in ALEVE® NIGHTTIME?
Medicinal ingredients: Naproxen sodium, Diphenhydramine hydrochloride
Non-medicinal ingredients: carnauba wax, FD&C Blue # 2 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, talc and titanium dioxide.

ALEVE® NIGHTTIME comes in the following dosage forms:
Caplet: naproxen sodium 220 mg / diphenhydramine hydrochloride 25mg.

Do not use ALEVE® NIGHTTIME if:
You have or are:
- pain that does not keep you from sleeping

- sleeplessness but are not in pain
- allergic to naproxen, naproxen sodium, diphenhydramine hydrochloride or any ingredient in the product
- allergic to acetylsalicylic acid (ASA), other salicylates or other non-steroidal anti-inflammatory drugs (NSAIDs)
- an active peptic ulcer, a history of recurrent ulceration, or active gastrointestinal bleeding
- inflammatory bowel disease
- liver disease (active or severe)
- kidney disease (severe or worsening)
- right before or after heart surgery
- in your third trimester of pregnancy because it may cause problems in the unborn child or complications during delivery
- do not have time for a full night's sleep
- elderly, as this drug may cause excitation rather than sedation
- taking with any other product containing diphenhydramine, even one used on skin

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

Have or have had:

- asthma or a similar respiratory illness
- diabetes
- nasal polyps
- itchy skin and hives
- history of gastrointestinal disease
- high blood pressure
- a blood clotting disorder
- heart disease/failure
- difficulty urinating due to enlarged prostate gland
- glaucoma
- any other serious condition
- sleeplessness due to mild to moderate pain persists continually for more than 5 days

Are:

- trying to conceive
- pregnant or breastfeeding
- older than age 65
- taking sedatives or tranquilizers
- taking any other drug

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

Stomach bleeding warning: This may cause stomach bleeding.
Symptoms may include:

- feeling faint, vomiting blood, bloody or black stools.

The chance of stomach bleeding is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take with other drugs containing an NSAID like acetylsalicylic acid (ASA), ibuprofen, naproxen, or prescription anti-inflammatory drugs
- have 3 or more alcoholic drinks every day while using this product.

Other warnings you should know about:

- The use of NSAIDs, like Aleve® Nighttime, in the second trimester of pregnancy should be restricted to the lowest dose necessary for shortest possible duration.
- At 20 weeks or later in pregnancy, your use of Aleve® Nighttime may need to be monitored by a doctor due to the rare risk of kidney problems in the unborn baby which may result in decreased amniotic fluid volume and other complications

Allergy alert: Stop use and get medical help right away if you have ▪hives ▪swelling of eyes and mouth ▪wheezing ▪shock ▪skin reddening ▪blisters ▪rash

When using this product:

- risk of heart attack or stroke may increase if you use more than directed or for longer than directed
- avoid drinking alcohol

Stop use and ask a doctor if:

- fever lasts more than 3 days
- pain and sleeplessness lasts more than 5 days or if your symptoms change
- symptoms get worse or new ones appear

Driving and using machines: If you become drowsy, dizzy or lightheaded do not drive or operate machinery and contact your doctor or pharmacist.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
The following may interact with ALEVE® NIGHTTIME:

- Anticoagulants (to decrease blood clotting)

- Antihistamines, tranquilizers, alcohol or other sedating drugs
- Antihypertensive drugs for your heart (including ACE inhibitors and beta-blockers)
- Cyclosporine
- Diuretics (“water pills”)
- Glucocorticoids
- Lithium
- Low dose ASA for doctor supervised daily preventative therapy (e.g. ASPIRIN® 81mg)
- Methotrexate
- NSAIDs or other pain medications (e.g. ibuprofen, acetaminophen)

Do not use this product if you are taking acetylsalicylic acid (ASA) for preventive therapy without talking to a doctor or pharmacist. Naproxen sodium may interfere with the preventive benefits of ASA.
Taking ALEVE® NIGHTTIME with a meal may slightly delay its absorption.

How to take ALEVE® NIGHTTIME:
Drink a full glass of water with each dose. Do not use in children under 12 years.

Usual dose:
Adults and children ≥12 years: 2 tablets at bedtime. Do not take more than 2 tablets in a 24 hour period.

Overdose:

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

Missed Dose:

Take once at night before bedtime. If you miss one night’s dose, do not take twice the recommended dose on the next night.

What are possible side effects from using ALEVE® NIGHTTIME?
These are not all the possible side effects you may have when taking ALEVE® NIGHTTIME. If you experience any side effects not listed here, tell your healthcare professional.
Like all medicines, ALEVE® NIGHTTIME may occasionally produce unwanted side effects. Stop use and contact a doctor or pharmacist if you experience: heartburn, nausea, vomiting, ringing or buzzing in the ears, bloating, redness or swelling is present in the painful area, choking sensation, diarrhea or constipation.

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Abdominal pain	✓		
UNCOMMON			
Black stools			✓
Hives			✓
Itching			✓
Rash			✓
Skin reddening			✓
Feel faint			✓
RARE			
Facial Swelling			✓
Fluid retention			✓
Vomiting blood			✓
VERY RARE			
Change in vision			✓
Difficulty Breathing			✓
Shock			✓
Chest pain			✓

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

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Store at 15-30ºC.

CAUTION: Contains enough drug to seriously harm a child. **KEEP OUT OF REACH AND SIGHT OF CHILDREN.**

If you want more information about ALEVE® NIGHTTIME:

- Talk to your healthcare professional

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html ; the manufacturer's website http://www.bayer.ca.

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