PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pain Reliever & Sleep Aid

Naproxen Sodium 220 mg and Diphenhydramine Hydrochloride 25 mg Tablets

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Pain Reliever & Sleep Aid (naproxen sodium and diphenhydramine hydrochloride tablets) is a non - prescription analgesic and sleep aid preparation to be taken as a single dose of 2 tablets at bedtime. Pain Reliever & Sleep Aid 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

Pain Reliever & Sleep Aid 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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- In self-medication, Pain Reliever & Sleep Aid 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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

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	Hypromellose, indigotine Al Lake 12-14% (Blue #2), magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol, silicon dioxide, stearic acid and titanium dioxide.

Pain Reliever & Sleep Aid Caplets are Blue, capsule shape, biconvex coated tablet. Engraved "220/25" on one side, "APO" on the other side and are available as bottles of 20 and 40 and bottle cartons of 20 and 40.

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 9.4 Drug-Drug Interactions section of the product monograph).

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 naproxen sodium 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.

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).

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs such as naproxen sodium. 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 9.4 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 Pain Reliever & Sleep Aid 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.

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 naproxen sodium and diphenhydramine hydrochloride tablets was analyzed through clinical trials which were performed during the course of the naproxen sodium and diphenhydramine hydrochloride tablets clinical development program. The clinical development program included a total of 3 randomized, double-blind studies and used naproxen sodium and diphenhydramine hydrochloride tablets in single or multiple doses. In total 678 subjects were treated with naproxen sodium and diphenhydramine hydrochloride tablets while 257 took naproxen sodium 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% to < 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 naproxen sodium and diphenhydramine hydrochloride tablets was analyzed through clinical trials which were performed during the course of the naproxen sodium and diphenhydramine hydrochloride tablets 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 naproxen sodium and diphenhydramine hydrochloride tablets in single or multiple doses. In total 678 subjects were treated with naproxen sodium and diphenhydramine hydrochloride tablets while 257 took naproxen sodium 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 2 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 naproxen sodium and diphenhydramine hydrochloride tablets with a frequency > 1% in clinical trials.

	Naproxen sodium and diphenhydramine hydrochloride tablets N = 785 (%)	Naproxen sodium 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

8.4 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
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	Rare	peripheral edema, particular

disorders	≥ 0.01% - < 0.1%	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 Pain Reliever & Sleep Aid. (See 7 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 Pain Reliever & Sleep Aid 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 (81 mg to 325 mg daily, for cardiovascular protection e.g. ASPIRIN* 81 mg)	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
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 to 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 to 4.80) in subjects taking OTC-dose ibuprofen and low dose ASA; the corresponding ratio for naproxen as monotherapy was 1.54 (1.04 to 2.28) which is not significantly different from the combined therapy. The corresponding ratio for ibuprofen as monotherapy was 1.38 (1.07 to 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. Naproxen sodium 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 (C_{max}) of 53 to 66 g/mL is reached approximately 1 to 1½ hours after intake of 440 mg naproxen sodium. For naproxen sodium caplets, food can slightly delay naproxen absorption but not the extent, and for naproxen sodium liquid gel capsules, 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 mcg/mL.

Diphenhydramine hydrochloride

Diphenhydramine hydrochloride is well-absorbed following oral administration but undergoes first-pass metabolism in the liver and only about 40 to 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 to 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 to 366 L. 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 to 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 to 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 to 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 to 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 at 20 to 25°C (68 to 77°F). Avoid exposure to high humidity and excessive heat above 40°C (104°F).

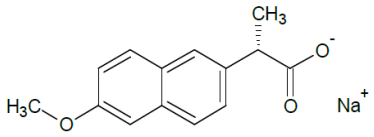
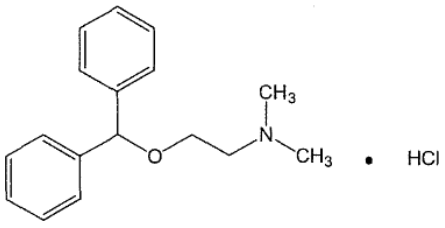
12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Naproxen sodium
Chemical name:	1. 2-Napthaleneacetic acid, 6-methoxy –α -methyl-, sodium salt, (S)-; 2. (-)-Sodium (S)-6-methoxy-α-methyl-2-naphthaleneacetate.
Molecular formula and molecular mass:	$C_{14}H_{13}NaO_3$; 252.24 g/mol
Structural formula:	
Physicochemical properties:	Naproxen sodium is a white to creamy white, crystalline powder, soluble in water and in methanol; sparingly soluble in alcohol; very slightly soluble in acetone; and practically insoluble in chloroform and in toluene, with a melting point of about 244 to 246°C (crystals from acetone) and 255°C with decomposition.
Proper name:	Diphenhydramine hydrochloride
Chemical name:	Ethanamine, 2-(diphenylmethoxy)-N,N-dimethyl-, hydrochloride. Other names: 2-(Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride
Molecular Formula and molecular mass:	$C_{17}H_{21}NO \cdot HCl$; 291.82 g/mol
Structural Formula:	
Physiochemical 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 166°C to 170°C (crystals from absolute alcohol & ether) and 167°C to 172°C (crystals from IPA acidified with HCl)

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Studies with Naproxen Sodium

The published trials regarding the efficacy of naproxen sodium 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 220 mg and 440 mg 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 naproxen sodium and diphenhydramine hydrochloride tablets consist of 1 multicenter, randomized, double-blind, parallel-group study designed to assess the efficacy of a single oral dose of naproxen sodium and diphenhydramine hydrochloride tablets 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 $\geq$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 naproxen sodium and diphenhydramine hydrochloride tablets 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 to 48.

14.2 Study Results

Table 5 - Summary of Patient Demographics for Pivotal Clinical Trial

Study Ref. Indication	Trial design & Indication	Duration	Dose (mg) naproxen sodium and diphenhydramine hydrochloride tablets & Comparators	Study subjects	Mean age (SD)	Gender M/F
Buchanan 14837	MC, R, DB, SD Extraction of 2-4 molars	10 hours	Naproxen sodium and diphenhydramine hydrochloride tablets 440 mg/50 mg (2 x 220 mg / 25 mg) Naproxen Sodium 440 mg (2 x 220 mg) DPH 50 mg (2 x 25 mg)	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 naproxen sodium and diphenhydramine hydrochloride tablets (A), naproxen sodium (B) and DPH (C)				
		Naproxen sodium and diphenhydramine hydrochloride tablets	Naproxen sodium	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

[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 naproxen sodium and diphenhydramine hydrochloride as a pain relieve was assess via Global Assessment of the Investigational Product as a Sleep Aid, where 0 = poor and 4 = excellent.

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 naproxen sodium and diphenhydramine hydrochloride tablets provides fast and effective pain relief and relieves occasional sleeplessness associated with minor aches and pain.

The safety data for naproxen sodium and diphenhydramine hydrochloride tablets is derived from single-dose and multiple-dose clinical trials. In the clinical trials for naproxen sodium and diphenhydramine hydrochloride tablets, the most common adverse reactions were nausea, headache, dizziness and vomiting, occurring in a small percentage of subjects, with no difference between naproxen sodium and diphenhydramine hydrochloride tablets, naproxen sodium, 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, naproxen sodium and diphenhydramine hydrochloride is an effective analgesic plus sleep-aid suitable for the relief of occasional sleeplessness associated with minor aches and pain.

14.3 Comparative Bioavailability Studies

A randomized, single-dose, double-blinded, two-way crossover comparative bioavailability study was conducted under fasting conditions on healthy male volunteers. The rate and extent of absorption of naproxen and diphenhydramine were measured and compared following a single oral dose (2 x 220 mg/25 mg tablets) of Pain Reliever & Sleep Aid tablets, 220 mg/25 mg (Apotex Inc.) and ALEVE® NIGHTTIME tablets, 220 mg/25 mg (Bayer Inc.). The results obtained from the 30 volunteers who completed the study are summarized in the following tables.

Naproxen (2 x 220 mg naproxen sodium/25 mg diphenhydramine hydrochloride) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Mean**	**90% Confidence Interval**
AUC_T (mcg·h/mL)	1032.10 1048.41 (17.0)	1027.52 1041.02 (15.7)	100.4	98.3 - 102.7
AUC_I (mcg·h/mL)	1101.90 1126.78 (21.7)	1095.56 1114.80 (18.2)	100.6	98.2 - 103.1
C_{max} (mcg/mL)	67.36 67.85 (12.2)	68.67 69.00 (9.1)	98.1	93.9 - 102.5
T_{max}§ (h)	1.87 (56.8)	1.57 (59.4)		
$T_{1/2}$§ (h)	18.53 (28.4)	18.08 (14.7)		

* Pain Reliever & Sleep Aid (naproxen sodium and diphenhydramine hydrochloride) tablets, 220 mg/25 mg (Apotex Inc.)

† ALEVE® NIGHTTIME (naproxen sodium and diphenhydramine hydrochloride) tablets, 220 mg/25 mg (Bayer Inc.) was purchased in Canada.

§ Expressed as arithmetic mean (CV%) only.

Diphenhydramine (2 x 220 mg naproxen sodium/25 mg diphenhydramine hydrochloride) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Mean**	**90% Confidence Interval**
AUC_T (ng·h/mL)	902.61 971.57 (40.8)	925.91 987.83 (37.8)	97.5	90.6 - 104.9
AUC_I (ng·h/mL)	925.08 997.97 (41.5)	950.48 1016.15 (38.5)	97.3	90.4 - 104.8
C_{max} (ng/mL)	75.54 79.81 (36.4)	77.16 80.64 (31.1)	97.9	88.9 - 107.9
T_{max}§ (h)	3.44 (32.0)	3.20 (29.8)		
$T_{1/2}$§ (h)	12.86 (20.4)	13.28 (20.7)		

Diphenhydramine (2 x 220 mg naproxen sodium/25 mg diphenhydramine hydrochloride) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Mean**	**90% Confidence Interval**
* Pain Reliever & Sleep Aid (naproxen sodium and diphenhydramine hydrochloride) tablets, 220 mg/25 mg (Apotex Inc.) † ALEVE® NIGHTTIME (naproxen sodium and diphenhydramine hydrochloride) tablets, 220 mg/25 mg (Bayer Inc.) was purchased in Canada. § Expressed as arithmetic mean (CV%) only.				

A single dose, 4-way pharmacokinetic study of 2 x naproxen sodium and diphenhydramine hydrochloride (220 mg naproxen sodium / 25 mg DPH), 2 x naproxen sodium tablets (220 mg naproxen sodium) and 2 x diphenhydramine hydrochloride (DPH 25 mg) 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 220 mg naproxen sodium) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Naproxen sodium and diphenhydramine hydrochloride**	**Naproxen sodium**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (mcg·hr/mL)	903.4 913.2 (14.87)	900.7 909.1 (13.73)	100.30	98.7, 102.0
AUC_I (mcg·hr/mL)	1053 1063 (14.76)	1052 1060 (13.87)	100.10	99.8, 105.2
C_{max} (mcg/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 25 mg DPH) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Naproxen sodium and diphenhydramine hydrochloride**	**DPH**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (mcg·hr/mL)	570.6 613.9 (38.84)	556.8 598.2 (39.03)	102.47	97.6, 107.1
AUC_I (mcg·hr/mL)	602.4 646.5 (37.06)	589.7 636.4 (40.47)	102.15	97.1, 107.1
C_{max} (mcg/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]		
T½ (h)	10.96 (2.685)	10.85 (2.474)		

This single dose, 4-way pharmacokinetic study of 2 x naproxen sodium and diphenhydramine hydrochloride (220 mg naproxen sodium / 25 mg DPH), 2 x naproxen sodium tablets (220 mg naproxen sodium) and 2 x diphenhydramine hydrochloride tablets (25 mg DPH) was also conducted in 32 healthy volunteers (15 male; 17 female) under fed conditions. Results show that the C_{max} 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 naproxen sodium and diphenhydramine hydrochloride under fasting versus fed conditions is presented below:

Naproxen (2 x 220 mg naproxen sodium) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Naproxen sodium and diphenhydramine hydrochloride (fasting)**	**Naproxen sodium and diphenhydramine hydrochloride (fed)**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (mcg·hr/mL)	903.4 913.2 (14.87)	874.2 882.4 (13.51)	96.77	95.2, 98.4

Naproxen (2 x 220 mg naproxen sodium) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Naproxen sodium and diphenhydramine hydrochloride (fasting)**	**Naproxen sodium and diphenhydramine hydrochloride (fed)**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_I (mcg·hr/mL)	1053 1063 (14.76)	971.5 980.7 (14.15)	92.26	92.1, 97.0
C_{max} (mcg/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)		

Diphenhydramine (2 x 25 mg DPH) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Naproxen sodium and diphenhydramine hydrochloride (fasting)**	**Naproxen sodium and diphenhydramine hydrochloride (fed)**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (mcg·hr/mL)	570.6 613.9 (38.84)	639.6 685.3 (38.46)	112.09	107.6, 118.1
AUC_I (mcg·hr/mL)	602.4 646.5 (37.06)	664.7 709.5 (37.64)	110.34	108.2, 119.6
C_{max} (mcg/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 200 mg/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, 30 mg/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 to 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 LD_{50} 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ALEVE® NIGHTTIME (naproxen sodium 220 mg and diphenhydramine hydrochloride 25 mg tablets), submission control 271910, Product Monograph, Bayer Inc. (OCT 01, 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pain Reliever & Sleep Aid

Naproxen Sodium 220 mg and Diphenhydramine Hydrochloride 25 mg Tablets

Read this carefully before you start taking **Pain Reliever & Sleep Aid**. 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 **Pain Reliever & Sleep Aid**.

What is Pain Reliever & Sleep Aid used for?

- Trust Pain Reliever & Sleep Aid 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 Pain Reliever & Sleep Aid work?

Pain Reliever & Sleep Aid 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 Pain Reliever & Sleep Aid?

Medicinal ingredients: Naproxen sodium, Diphenhydramine hydrochloride

Non-medicinal ingredients: Hypromellose, indigotine Al Lake 12-14% (Blue #2), magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol, silicon dioxide, stearic acid and titanium dioxide.

Pain Reliever & Sleep Aid comes in the following dosage forms:

Caplet: naproxen sodium 220 mg / diphenhydramine hydrochloride 25 mg.

Do not use Pain Reliever & Sleep Aid 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 Pain Reliever & Sleep Aid. 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
- in your first or second trimester of pregnancy
- 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.

Other warnings you should know about:

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.

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 Pain Reliever & Sleep Aid:

- 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* 81 mg)
- 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 Pain Reliever & Sleep Aid with a meal may slightly delay its absorption.

How to take Pain Reliever & Sleep Aid:

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 Pain Reliever & Sleep Aid, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or 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 Pain Reliever & Sleep Aid?

These are not all the possible side effects you may have when taking Pain Reliever & Sleep Aid. If you experience any side effects not listed here, tell your healthcare professional. Like all medicines, Pain Reliever & Sleep Aid 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			√

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store at 20 to 25°C (68 to 77°F). Avoid exposure to high humidity and excessive heat above 40°C (104°F).

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

If you want more information about Pain Reliever & Sleep Aid:

- 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); manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

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