

PRODUCT MONOGRAPH

NAPROXEN SODIUM CAPSULES

220 mg

Non-steroidal anti-inflammatory drug

Analgesic, Antipyretic

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

Date of Revision:
October 14, 2020

Control No.: 243192

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION.....	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS.....	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	6
DRUG INTERACTIONS.....	9
DOSAGE AND ADMINISTRATION	11
OVERDOSAGE	12
ACTION AND CLINICAL PHARMACOLOGY.....	12
STORAGE AND STABILITY	13
SPECIAL HANDLING INSTRUCTIONS.....	13
DOSAGE FORMS, COMPOSITION AND PACKAGING	13
PART II: SCIENTIFIC INFORMATION	14
PHARMACEUTICAL INFORMATION.....	14
CLINICAL TRIALS	15
DETAILED PHARMACOLOGY.....	18
MICROBIOLOGY	18
TOXICOLOGY	18
REFERENCES	23
PART III: CONSUMER INFORMATION	35

NAPROXEN SODIUM CAPSULES

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Capsules 220 mg	Ammonium hydroxide, FD&C Blue #1, gelatin, glycerine, high polychain, lactic acid, mannitol polyethylene glycol, povidone, propylene glycol, purified water, shellac, simethicone, sorbitol sorbitan, titanium dioxide

INDICATIONS AND CLINICAL USE

NAPROXEN SODIUM CAPSULES are indicated for the reduction of fever and the treatment of pain:

- NAPROXEN SODIUM CAPSULES are clinically proven to relieve arthritis pain. NAPROXEN SODIUM CAPSULES relieve the daily pain and stiffness of arthritis. NAPROXEN SODIUM CAPSULES relieve morning stiffness and arthritis pain at rest, on passive motion, on weight bearing, pain experienced day or night due to arthritis
- NAPROXEN SODIUM CAPSULES help relieve the night pain associated with arthritis
- NAPROXEN SODIUM CAPSULES relieve the pain of inflammation
- NAPROXEN SODIUM CAPSULES relieve the pain or stiffness of rheumatic or arthritic conditions
- NAPROXEN SODIUM CAPSULES relieve joint and body pain
- NAPROXEN SODIUM CAPSULES relieve muscular ache
- NAPROXEN SODIUM CAPSULES relieve the pain of muscle sprains and strains
- NAPROXEN SODIUM CAPSULES relieve backache
- NAPROXEN SODIUM CAPSULES relieve headache
- NAPROXEN SODIUM CAPSULES relieve migraine pain
- NAPROXEN SODIUM CAPSULES relieve the pain of menstrual cramps (dysmenorrhoea)
- NAPROXEN SODIUM CAPSULES relieve the pain of minor surgery
- NAPROXEN SODIUM CAPSULES relieve toothache
- NAPROXEN SODIUM CAPSULES relieve the pain of dental extractions
- NAPROXEN SODIUM CAPSULES relieve minor aches and pain associated with the common cold

CONTRAINDICATIONS

Naproxen sodium is contraindicated in patients

- who have previously exhibited allergy to naproxen sodium
- with known hypersensitivity to the active substance naproxen (including naproxen sodium) or any of the excipients in the capsules. For a complete listing, see the *Dosage Forms, Composition and Packaging* section of the product monograph
- 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
- when used right before or after heart surgery.

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.

Cardiovascular

Patients with severe cardiac impairment and a history of hypertension.

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).

Gastrointestinal

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

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 CAPSULES with warfarin requires close monitoring of the international normalized ratio (INR). Even with therapeutic INR monitoring, increased bleeding may occur.

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 CAPSULES. If patients experience such adverse reactions, they should exercise caution in carrying out activities that require alertness, like driving or using machinery.

Respiratory

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

Skin

Patients with a medical history of urticaria and angioedema.

Fertility Impairment

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.

Special Populations:

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.

Pregnant Women:

Caution should be exercised in prescribing NAPROXEN SODIUM CAPSULES 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.

Nursing Women:

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.

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.

Persons on a Low Sodium Diet:

One capsule 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.

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).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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

The safety profile of naproxen sodium was analysed through a meta-analysis of the clinical trials which were performed in the course of the naproxen sodium clinical development program. The meta-analysis included a total of 46 studies, which satisfied the criteria of being randomized, placebo controlled, double-blind and used naproxen sodium in single (SD, 220 mg or 440 mg pooled data), multiple (MD, 440 mg/day and 880 mg/day) or PRN (up to 880 mg/day) doses. In total 4623 subjects were treated with naproxen sodium while 2659 took placebo. Fifty-two percent of subjects participated in SD trials, 20 % in MD trials all lasting for 7 days and the remaining 28% in PRN trials. They were predominantly Caucasian, slightly more women with a mean age between the 20s and 30s with exception of 422 patients from the arthritis studies with a mean age in the low 60s. The occurrence of all adverse events did not differ between naproxen sodium and placebo, in the SD, MD or PRN trials. Moderate and severe events tended to occur less frequently in the subjects treated with naproxen sodium MD compared to placebo, presumably due to concomitant treatment of naturally occurring headache. The data in table 1 shows the frequencies of adverse events that are > 1% from the meta-analysis. A thorough evaluation of gastrointestinal adverse events showed no difference between naproxen sodium and placebo. There was no serious gastrointestinal adverse event (bleeding or perforation) or any case of anaphylaxis.

Table 1. Adverse events that occurred with naproxen sodium (low dose short duration) with a frequency > 1% in clinical trials.

	Naproxen Sodium n= 4623 (%)	Placebo n= 2659 (%)
Gastrointestinal		

Dyspepsia	1.9%	1.8%
Nausea	4.4 %	4.8%
Vomiting	1.8%	2.4%
Nervous System		
Dizziness	2.0%	2.1%
Headache	4.9%	6.8%
Somnolence	2.4%	1.5%

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

Gastrointestinal: Constipation Diarrhea

Other

Allergic reactions Edema Rash/pruritus

Post-Market Adverse Drug Reactions

Table 2. 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 disorders	Very rare < 0.01% and isolated reports	Anaphylaxis/anaphylactoid reactions
Blood and the lymphatic system disorders	Very rare < 0.01% and isolated reports	hematopoietic disturbances (leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia, eosinophilia, hemolytic anemia)
Psychiatric disorders	Very rare < 0.01% and isolated reports	psychiatric disorders
Nervous system disorders	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 disorders	Very rare < 0.01% and isolated reports	visual disturbance, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema
Ear & labyrinth disorders	Uncommon ≥ 0.1 % - < 1 %	vertigo
	Very rare < 0.01% and isolated reports	hearing impairment, tinnitus
Cardiac disorders	Very rare < 0.01% and isolated reports	congestive heart failure, hypertension, pulmonary edema

Table 2. 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.

Vascular disorders	Very rare < 0.01% and isolated reports	vasculitis
Respiratory, Thoracic and Mediastinal disorders	Very rare < 0.01% and isolated reports	dyspnea, asthma, eosinophilic pneumonitis
Gastrointestinal disorders	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 disorders	Very rare < 0.01% and isolated reports	hepatitis, icterus
Skin & subcutaneous tissue disorders	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 disorders	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 system and breast disorders	Very rare < 0.01% and isolated reports	female infertility

Table 2. 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.

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.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

The drugs listed in table 3 are based on either drug interaction case reports or studies.

Table 3 - 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
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.

Low-dose acetylsalicylic acid:

In a recent (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 recent (2006) 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 mono-therapy was 1.54 (1.04-2.28) which is not significantly different from the combined therapy. The corresponding ratio for ibuprofen as mono-therapy 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 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 therapy. The clinical relevance of this interaction is not known. Treatment with 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, hydantoines, probenecid, zidovudine.

Drug-Food Interactions

Peak naproxen levels were reached at 1.4 hours on an empty stomach and at 3.7 hours with a meal.

Drug-Herb Interactions

Interactions with herbal products have not been established

Drug-Laboratory 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).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- In self-medication, NAPROXEN SODIUM CAPSULES should only be used for a short term treatment period of up to five days for pain and 3 days for fever. 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.
- NAPROXEN SODIUM CAPSULES are as safe on the stomach as acetaminophen extra strength 500 mg and Ibuprofen 200mg if the maximum daily dose and the recommended length of use for each product is not exceeded.
- NAPROXEN SODIUM CAPSULES provide non-prescription pain relief that lasts up to 12 hours with 1 pill.

Recommended Dose and Dosage Adjustment

Adults (12 to 65 years): 1 capsule every 8 to 12 hours. For individuals over 65 years, 1 capsule every 12 hours. Do not take more than 2 capsules in a 24 hour period. Drink a full glass of water with each dose.

Under 12 years: Children under 12 should not take this drug. The safety in pediatric use has not been established.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 principle mechanism of action relies on the inhibition of prostaglandin synthesis. Prostaglandins are naturally occurring fatty acids derivatives 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.

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.

Pharmacokinetics

Table 4 Summary of naproxen sodium's pharmacokinetic parameters in healthy subjects

Single dose	C _{max} mcg/ml	t _{1/2} hours	AUC _{0-∞} mcg/ml.h	Clearance l/h	Volume of distribution (l)
220 mg	35	18	546	0.4	10.0
440 mg	66	18	1021	0.4	10.6
2 x 220 mg	53	18.6	852	0.5	14.1

Absorption: 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 440mg naproxen sodium. 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.

Distribution: 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.

Metabolism: 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.

Excretion: 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.

Special Populations and Conditions

Geriatrics: There is no evidence of differential metabolism or excretion in the elderly.

Gender: 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.

STORAGE AND STABILITY

Store at 15°C to 25°C, avoid high humidity and excessive heat over 40°C.

SPECIAL HANDLING INSTRUCTIONS

No special requirements

DOSAGE FORMS, COMPOSITION AND PACKAGING

NAPROXEN SODIUM CAPSULES: A clear, blue oblong gelatin capsule printed with logo “220” in white ink. Each capsule of NAPROXEN SODIUM CAPSULES contains 220 mg of naproxen sodium, of which 20 mg is sodium. The excipients consist of ammonium hydroxide, FD&C Blue #1, gelatin, glycerine, high polychains, lactic acid, mannitol, polyethylene glycol, povidone, propylene glycol, purified water, shellac, simethicone, sorbitol sorbitan, titanium dioxide.

Available in bottles of 20, 40 80 capsules. This package is child-resistant.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

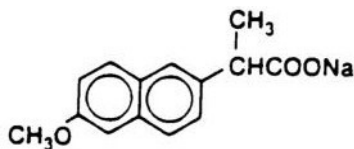
Drug Substance

Proper name: Naproxen sodium

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

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, crystalline solid, freely soluble in water with a melting point of about 255°C with decomposition.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single-dose, double-blinded, standard, 2-way, crossover comparative bioavailability study conducted under fasting conditions was performed on healthy male volunteers. The results obtained from 26 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of naproxen sodium were measured and compared following a single oral dose (1 x 220 mg) of NAPROXEN SODIUM CAPSULES (naproxen sodium) 220 mg capsules (Apotex Inc.) and ALEVE® Liquid Gels (naproxen sodium) 220 mg capsules (Bayer Inc.).

Naproxen (1 x 220 mg) From Measured Data				
Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC _t (mcg•h/mL)	582.23 585.86 (10.4)	567.95 572.69 (13.1)	102.51	100.32-104.75
AUC _t (mcg•h/mL)	616.77 621.84 (12.0)	600.57 607.10 (14.7)	102.70	100.38-105.07
C _{max} (mcg/mL)	43.58 44.01 (17.5)	42.19 42.62 (17.9)	103.31	96.29-110.83
T _{max} § (h)	1.21 (60.2)	1.25 (79.8)		
T _{1/2} § (h)	17.93 (11.9)	17.75 (11.4)		
* NAPROXEN SODIUM CAPSULES (naproxen sodium) 220 mg capsules (Apotex Inc.).				
† ALEVE® Liquid Gels (naproxen sodium) 220 mg capsules (Bayer Inc.) were purchased in Canada.				
§ Expressed as arithmetic means (CV%) only.				

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.

Study Ref. Indication	Trial design & Indication	Duration	Dose (mg) Naproxen Sodium & Comparator	Study subjects	Mean age (StD)	Gender M/F
Kiersch 1993	DB, R, PC, SD Extraction of 1-2 molars	12 hours	Naproxen Sodium 220 mg , Advil 200 mg, Placebo	203 healthy subjects	25 (7)	90/113
Fricke 1993	DB, R, PC, SD Extraction of 3-4 molars	12 hours	Naproxen Sodium 440 mg, Ibuprofen 400 mg, Placebo	201 healthy subjects	24 (7)	77/124
Kiersch 1994	DB, R, PC, SD Extraction of 3-4 molars	12 hours	Naproxen Sodium 440 mg, Acetaminophen Extra Strength 1000 mg, Placebo	226 healthy subjects	24 (5)	102/124
Schiff 2004 [DB, R, PC, MD Pain and stiffness of knee osteoarthritis	7 days	Naproxen Sodium 440 mg daily (220 mg morning & evening) Ibuprofen 1200 mg daily (400 mg TID) placebo	198 patients, ≥ 65 years knee osteoarthritis	72 (5)	75/123

Study demographics and trial design

The dental study population consisted of young, healthy subjects that required extraction of 1 to 4 molars. The knee osteoarthritis (OA) patients were in good general health, of both sexes and any race and had a mean age of 72 years. The diagnosis was verified by standard radiographic criteria applicable for OA stage I-III. All patients had episodic flare ups of OA with at least moderate pain.

Study results

Study	Endpoints	Associated values and statistical significance for Naproxen Sodium (A), Comparator (C) and Placebo (P)					
		Naproxen Sodium	Comparator	Placebo	A vs. C	A vs. P	C vs. P
Kiersch 1993	Pain relief up to 12 hours TOTPAR ¹	21.3	17.8	6.0	NS	< 0.001	< 0.001
	Onset of pain relief (median)	1 h	2 h	> 12 h	NS	< 0.001	< 0.001
	Time to re-medication (median)	9.4 h	8.0 h	2 h	NS	< 0.001	< 0.001
	Re-medication %	51 %	63 %	90 %	NS	< 0.001	< 0.001
Fricke 1993	Pain relief up to 12 hours TOTPAR ¹	19.6	15.8	3.5	NS	< 0.001	< 0.001
	Onset of pain relief (median)	0.7 h	0.7 h	> 12 h	NS	< 0.001	< 0.001
	Time to re-medication (median)	7 h	6 h	1.1 h	NS	< 0.001	< 0.001
	Re-medication %	64 %	78%	95%	(=0.056)	< 0.001	< 0.001

Kiersch 1994	Pain relief up to 12 hours TOTPAR ¹	19.1	8.3	5.7	< 0.001	< 0.001	NS
	Onset of pain relief (median)	2 h	2 h	> 12 h	NS	< 0.001	< 0.001
	Time to re-medication (median)	9.9 h	3.1 h	2.0 h	< 0.001	< 0.001	NS
	Re-medication %	56 %	90 %	90 %	< 0.001	< 0.001	NS
Schiff 2004	Symptom improvement on day 7:						
	• Pain at rest	0.8	0.8	0.5	NS	< 0.05	NS
	• Pain on passive motion	0.9	0.9	0.6	NS	< 0.05	NS
	• Pain on weight bearing	1.2	1.0	0.7	NS	(=0.064)	NS
	• Stiffness after rest	0.9	0.9	0.4	NS	< 0.05	NS
	• Day pain	1.0	1.0	0.4	NS	< 0.01	< 0.01
	• Night pain	1.0	0.8	0.5	NS	< 0.05	NS
	• 50-foot walk time	2.3 s	1.9 s	1.0 s	NS	< 0.05	NS

s = second(s)

h = hour(s)

The dental pain model, i.e. tooth extraction model, is accepted as the model of choice to establish analgesic efficacy and the results can be extrapolated to other pain states relevant for OTC medication. The studies demonstrate that naproxen sodium provides fast and effective pain relief.

For the short-term treatment of pain or stiffness of rheumatic or non-serious arthritic conditions naproxen sodium provides clear relief of such states. Naproxen sodium is clinically proven to relieve arthritis pain. In the comparison naproxen sodium /placebo and Ibuprofen/placebo, naproxen sodium was superior with respect to alleviating pain experienced at night and stiffness after rest.

¹ Total pain relief (TOTPAR) is an integrated (summary) pain score where pain relief is assessed hourly and represented on a 5-point scale and summed over a period of time (i.e. 12 hours). The 5-point scale consists of a zero score representing no pain relief, 1= a little, 2=some, 3= a lot and 4=complete pain relief

In dysmenorrhea naproxen sodium compared to placebo demonstrated a significant superiority with respect to total pain relief over 12 hours.

The naproxen sodium safety data is derived from clinical trials and post-marketing experience. naproxen sodium is as safe on the stomach as acetaminophen extra strength 500 mg and ibuprofen 200mg if the maximum daily dose and recommended length of use for each product is not exceeded. In the clinical trials the safety profile was comparable to that of ibuprofen, acetaminophen extra strength and placebo; the most common reactions were GI upset and dizziness, occurring in a small percentage of subjects, with no difference between placebo and active treatments. Serious adverse reactions, like gastrointestinal bleeding or anaphylactic shock, were very rare events (< 0.01%) and occurred in the same degree in naproxen sodium and ibuprofen as well as acetaminophen extra strength treated subjects.

Overall, NAPROXEN SODIUM CAPSULES are an effective analgesic suitable for the treatment of common ailments relevant for self-medication; NAPROXEN SODIUM CAPSULES relieve the daily pain and stiffness of arthritis. NAPROXEN SODIUM CAPSULES relieve morning stiffness and arthritis pain at rest, on passive motion, on weight bearing, pain experienced day or night due to arthritis.

DETAILED PHARMACOLOGY

Please refer to *Action and Clinical Pharmacology* section above.

MICROBIOLOGY

N/A

TOXICOLOGY

The oral LD₅₀ of the drug 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 hematopoiesis 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.

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.

Reproductive Studies

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.

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.

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.

REFERENCES

- Abrahams C, Levin NW. Analgesic nephropathy. *Lancet*. 1968 Mar 23;1(7543):645
- Adams SS, Bough RG, Cliffe EE, Lessel B, Mills RF. Absorption, distribution and toxicity of ibuprofen. *Toxicol Appl Pharmacol*. 1969 Sep;15(2):310-30.
- Ahern M, Booth J, Loxton A, McCarthy P, Meffin P, Kevat S. Methotrexate kinetics in rheumatoid arthritis: is there an interaction with nonsteroidal antiinflammatory drugs? *J Rheumatol*. 1988 Sep;15(9):1356-60.
- Aiken JW. Aspirin and indomethacin prolong parturition in rats: evidence that prostaglandins contribute to expulsion of fetus. *Nature*. 1972 Nov 3;240(5375):21-5
- Ailabouni W, Eknayan G. Nonsteroidal anti-inflammatory drugs and acute renal failure in the elderly. A risk-benefit assessment. *Drugs Aging*. 1996 Nov;9(5):341-51.
- Anonymous. Analgesic and anti-inflammatory drugs. In Reynolds ed. *Martindale. The Extra Pharmacopoeia*. 1989; 1:25-6.
- Anzellotti P et al. Low-dose naproxen interferes with the antiplatelet effects of aspirin in healthy subjects: recommendations to minimize the functional consequences. *Arthritis Rheum*. 2011;63: 850- 859.
- Arnold R, Heimpel H. Aplastic anaemia after naproxen? *Lancet*. 1980 Feb 9;1(8163):321.
- Atta MG, Whelton A. Acute renal papillary necrosis induced by ibuprofen. *Am J Ther*. 1997 Jan;4(1):55-60.
- Baldwin AC, Stevenson SW, Dudley GA. Nonsteroidal anti-inflammatory therapy after eccentric exercise in healthy older individuals. *J Gerontol A Biol Sci Med Sci*. 2001 Aug;56(8):M510-3.
- Bansal V, Dex T, Proskin H, Garreffa S. A look at the safety profile of over-the-counter naproxen sodium: a meta-analysis. *J Clin Pharmacol*. 2001 Feb;41(2):127-38.
- Bareille MP, Montastruc JL, Lapeyre-Mestre M. Liver damage and NSAIDs. *Therapie* 2001; 56:51-55.
- Barrera JE, Meyers AD, Hartford EC. Hypopharyngeal stenosis and dysphagia complicating toxic epidermal necrolysis.
- Arch Otolaryngol Head Neck Surg*. 1998 Dec;124(12):1375-6.
- Barry M, Howe J, Back D, Breckenridge A, Brettle R, Mitchell R et al. The effects of indomethacin and naproxen on zidovudine pharmacokinetics. *Br J Clin Pharmacol*. 1993 Jul;36(1):82-5.
- Becker-Cohen R, Frishberg Y. Severe reversible renal failure due to naproxen-associated acute interstitial nephritis. *Eur J Pediatr*. 2001 May;160(5):293-5.

Biskupiak JE, Brixner DI, Howard K, Oderda GM. Gastrointestinal complications of over-the-counter nonsteroidal antiinflammatory drugs. *J Pain Palliat Care Pharmacother.* 2006;20(3):7-14

Bosseckert H. NSAR-nebenwirkungen am dünn darm und am kolon. *Verdauungskrankheiten.* 2000; 18(4):160-165.

Boulinguez S, Cornee-Leplat I, Bouyssou-Gauthier ML, Bedane C, Bonnetblanc JM. Analysis of the literature about drug-induced aphthous ulcers *Ann Dermatol Venereol.* 2000 Feb;127(2):155-8.

Boulinguez S, Reix S, Bedane C, Debrock C, Bouyssou-Gauthier ML, Sparsa A et al. Role of drug exposure in aphthous ulcers: a case-control study. *Br J Dermatol.* 2000 Dec;143(6):1261-5.

Boyd EM. The acute oral toxicity of acetylsalicylic acid. *Toxicology.* 1959 May;1(3):229-39.

Brenna E, Sandvik AK, Kleveland PM, Waldum HL. Tykktarmsskader av ikke-steroid antiinflammatoriske medikamenter. 1995; 115:1225-7.

Brezin JH, Katz SM, Schwartz AB, Chinitz JL. Reversible renal failure and nephrotic syndrome associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med.* 1979 Dec 6;301(23):1271-3.

Bridges AJ, Marshall JB, Diaz-Arias AA. Acute eosinophilic colitis and hypersensitivity reaction associated with naproxen therapy. *Am J Med.* 1990 Oct;89(4):526-7.

Burns JJ, Yu TF, Dayton PG, Gutman AB, Brodie BB. Biochemical pharmacological considerations of phenylbutazone and its analogues. *Ann N Y Acad Sci.* 1960 Mar 30;86:253-91.

Capone M et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. *J Am Coll Cardiol* 2005; 45 (8): 1295-30.

Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345(25):1809-17.

Celis H, Thijs L, Staessen JA, Birkenhager WH, Bulpitt CJ, de Leeuw PW, et al. Interaction between nonsteroidal anti-inflammatory drug intake and calcium-channel blocker-based antihypertensive treatment in the Syst-Eur trial. *J Hum Hypertens.* 2001 Sep;15(9):613-8.

Chan TY. Severe asthma attacks precipitated by NSAIDs. *Ann Pharmacother.* 1995 Feb;29(2):199.

Chapman P. Naproxen and sudden hearing loss. *J Laryngol Otol.* 1982 Feb;96(2):163-6.

Chester R, Dukes M, Slater SR, Walpole AL. Delay of parturition in the rat by anti-inflammatory agents which inhibit the biosynthesis of prostaglandins. *Nature.* 1972 Nov 3;240(5375):37-8.

Chudwin DS, Strub M, Golden HE, Frey C, Richmond GW, Luskin AT. Sensitivity to non-acetylated salicylates in a patient with asthma, nasal polyps, and rheumatoid arthritis. *Ann Allergy.* 1986 Aug;57(2):133-4.

Clausen E. Histological changes in rabbit kidneys induced by phenacetin and Acetylsalicylic acid. *Lancet*. 1964 Jul 18;18:123-4.

Court H, Volans GN. Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev*. 1984 Spring;3(1):1-21.

Creemers MC, Chang A, Franssen MJ, Fiselier TJ, van Riel PL. Pseudoporphyria due to naproxen. A cluster of 3 cases. *Scand J Rheumatol*. 1995;24(3):185-7.

Csapo AI, Csapo EF, Fay E, Henzl MR, Salau G. The delay of spontaneous labor by Naproxen in the rat model. *Prostaglandins*. 1973 Jun;3(6):827-37.

Csapo AI, Csapo EF, Fay E, Henzl MR, Salau G. The role of estradiol 17 in the activation of the uterus during premature labor and the effect of Naproxen, an inhibitor of prostaglandin synthesis. *Prostaglandins*. 1973 Jun;3(6):839-46.

Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. *Arch Intern Med*. 2002 Oct 28;162(19):2204-8.

Cryer B, Berlin RG, Cooper SA, et al. Double-blind, randomized, parallel, placebo-controlled study of ibuprofen effects on thromboxane B2 concentrations in aspirin-treated healthy adult volunteers. *Clin Ther* 2005;27(2):185-91.

Davies NM, Anderson KE. Clinical pharmacokinetics of naproxen. *Clin Pharmacokinet*. 1997 Apr;32(4):268-93.

Davis A, Day RO, Begg EJ. Interactions between non-steroidal anti-inflammatory drugs and antihypertensives and diuretics. *Aust N Z J Med*. 1986 Aug;16(4):537-46.

De Broe ME, Elseviers MM. Analgesic nephropathy. *N Engl J Med*. 1998 Feb 12;338(7):446-52.

De Silva B, Banney L, Uttley W, Luqmani R, Schofield O. Pseudoporphyria and nonsteroidal antiinflammatory agents in children with juvenile idiopathic arthritis. *Pediatr Dermatol*. 2000 Nov-Dec;17(6):480-3.

DeArmond B, Francisco CA, Lin JS, Huang FY, Halladay S, Bartziek RD et al. Safety profile of over-the-counter naproxen sodium. *Clin Ther*. 1995 Jul-Aug;17(4):587-601.

Drugdex. Cyclosporine. Micromex 2004.

Drugdex. Lithium. Micromex 2004.

Drugdex. Naproxen. Micromex 2004

Du Ville L, Debeuckelaere S, Reynaert H, Devis G. Pancreatitis associated with naproxen. *Am J Gastroenterol*. 1993 Mar;88(3):464.

Dudley GA, Czerkawski J, Meinrod A, Gillis G, Baldwin A, Scarpone M. Efficacy of naproxen sodium for exercise-induced dysfunction muscle injury and soreness. *Clin J Sport Med.* 1997 Jan;7(1):3-10.

Ellis DJ, Brown CA, Kamm BR, Taylor LA, Yang DS, Roe RL. Effects of naproxen on bleeding time and platelet function in normal subjects. *Clin Pharmacol Ther.* 1980;27:247.

Ericson A, Kallen BA. Nonsteroidal anti-inflammatory drugs in early pregnancy. *Reprod Toxicol.* 2001 Jul-Aug;15(4):371-5.

Evans JM, McGregor E, McMahon AD, McGilchrist MM, Jones MC, White G et al. Non-steroidal anti-inflammatory drugs and hospitalization for acute renal failure. *QJM.* 1995 Aug;88(8):551-7.

Feenstra J, Heerdink ER, Grobbee DE, Stricker BH. Association of nonsteroidal anti-inflammatory drugs with first occurrence of heart failure and with relapsing heart failure: the Rotterdam Study. *Arch Intern Med.* 2002 Feb 11;162(3):265-70.

Fraunfelder FT, Samples JR, Fraunfelder FW. Possible optic nerve side effects associated with nonsteroidal anti-inflammatory drugs. *J Toxicol Cutaneous Ocul Toxicol.* 1994; 13:311-6.

Frenia ML, Long KS. Methotrexate and nonsteroidal antiinflammatory drug interactions. *Ann Pharmacother.* 1992 Feb;26(2):234-7.

Fricke JR et al. Efficacy and safety of naproxen sodium and ibuprofen for pain relief after oral surgery. *Curr Ther Res.* 1993;54:619-27.

Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. *Am J Cardiol.* 2002 Mar 21;89(6A):18D-25D.

Garcia Rodriguez LA, Williams R, Derby LE, Dean AD, Jick H. Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. *Arch Intern Med.* 1994 Feb 14;154(3):311-6.

Gebhardt M, Wollina U. Kutane Nebenwirkungen nichsteroidaler antiphlogistika (NSAID). *Z Rheumatol.* 1995; 54:405-412.

Golden HE, Moskowitz RW, Minic M. Analgesic efficacy and safety of nonprescription doses of naproxen sodium compared with acetaminophen in the treatment of osteoarthritis of the knee. *Am J Ther.* 2004 Mar-Apr;11(2):85-94.

Goodman & Gilman's *The Pharmacological Basis of Therapeutics* Editors: Joel Hardman, Lee Limbird, A.G. Goodman Tenth Edition, Chapter 27 "Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout" Authors: L. Jackson Roberts II and Jason D. Morrow Pages: 687-731

Goodwin SD, Glenn RW. Nonsteroidal anti-inflammatory drug-associated pulmonary infiltrates with eosinophilia. Review of the literature and Food and Drug Administration Adverse Drug

Reaction reports. Arch Intern Med. 1992 Jul;152(7):1521-4.

Grattan CEH et al. Naproxen induced erythema nodosum. Br Med J. 1984; 288: 114.

Grennan DM, Jolly J, Holloway LJ, Palmer DG. Vasculitis in a patient receiving naproxen. N Z Med J. 1979 Jan 24;89(628):48-9.

Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol. 2000 Mar 1;151(5):488-96.

Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs. An update. Clin Pharmacokinet. 1990 Mar;18(3):210-9.

Hammerman C. Patent ductus arteriosus. Clinical relevance of prostaglandins and prostaglandin inhibitors in PDA pathophysiology and treatment. Clin Perinatol. 1995 Jun;22(2):457-79.

Health Canada Bureau of nutritional Sciences Food Directorate: Analysis of policy recommendations concerning the addition of vitamins and minerals to foods. October 1999.

Health Canada: Chapter 3: nutrition intervention in hepatitis C. Hepatitis C: Nutrition care Canadian guidelines for health care providers.

Health Canada: Problem solver in hypertension management and control. The health heart kit. Helping your patients reduce their risk.

Healy CM, Thornhill MH. An association between recurrent oro-genital ulceration and non-steroidal anti-inflammatory drugs. J Oral Pathol Med. 1995 Jan;24(1):46-8.

Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med. 1998 May 25;158(10):1108-12.

Hernandez-Diaz S, Garcia-Rodriguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. Am J Med. 2001 Feb 19;110 Suppl 3A:20S-7S.

Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med. 2000 Jul 24;160(14):2093-9.

Hernandez-Diaz S, Rodriguez LA. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. J Clin Epidemiol. 2002 Feb;55(2):157-63.

Heymann WR, Lerman JS, Luftschein S. Naproxen-induced lichen planus. J Am Acad Dermatol. 1984 Feb;10(2 Pt 1):299-301.

Hitchens, J.T., Goldstein, S., Sambuca, A. & Shemano, I., Pharmacologist 9:242 (1967).

Hoppmann RA, Peden JG, Ober SK. Central nervous system side effects of nonsteroidal anti-inflammatory drugs. Aseptic meningitis, psychosis, and cognitive dysfunction. *Arch Intern Med.* 1991 Jul;151(7):1309-13.

Houston MC, Weir M, Gray J, Ginsberg D, Szeto C, Kahlunen PM, et al. The effects of nonsteroidal anti-inflammatory drugs on blood pressures of patients with hypertension controlled by verapamil. *Arch Intern Med.* 1995 May 22;155(10):1049-54.

Hughes JA, Sudell W. Hemolytic anemia associated with naproxen. *Arthritis Rheum.* 1983 Aug;26(8):1054.

Hunt PJ, Gibbons SS. Naproxen induced thrombocytopenia: a case report. *N Z Med J.* 1995 Nov 24;108(1012):483-4.

Ivey KJ, Rooney PJ. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. *Baillieres Clin Rheumatol.* 1989 Aug;3(2):393-409.

Jahangiri M, Jayatunga AP, Bradley JW, Goodwin TJ. Naproxen-associated vasculitis. *Postgrad Med J.* 1992 Sep;68(803):766-7.

Jain A, McMahon FG, Slattery JT, Levy G. Effect of naproxen on the steady-state serum concentration and anticoagulant activity of warfarin. *Clin Pharmacol Ther.* 1979 Jan;25(1):61-6.

Jamali F, Stevens DR. Naproxen excretion in milk and its uptake by the infant. *Drug Intell Clin Pharm.* 1983 Dec;17(12):910-1.

Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. *Arch Intern Med.* 2000 Mar 13;160(5):610-9.

Jiang HK, Chang DM. Non-steroidal anti-inflammatory drugs with adverse psychiatric reactions: five case reports. *Clin Rheumatol.* 1999;18(4):339-45.

Johnson AG, Seidemann P, Day RO. NSAID-related adverse drug interactions with clinical relevance. An update. *Int J Clin Pharmacol Ther.* 1994 Oct;32(10):509-32.

Johnson AG. NSAIDs and blood pressure. Clinical importance for older patients. *Drugs Aging.* 1998 Jan;12(1):17-27.

Johnson AG. NSAIDs and increased blood pressure. What is the clinical significance? *Drug Saf.* 1997 Nov;17(5):277-89.

Julou L, Ducrot R, Fournel J, Ganter P, Populaire P, Durel J, Myon J, Pascal S, Pasquet J. [Toxicologic study of methiazinic acid (16091 R.P)] *Arzneimittelforschung.* 1969 Aug;19(8):1207-14. French.

Kahn LH, Chen M, Eaton R. Over-the-counter naproxen sodium and esophageal injury. *Ann Intern Med.* 1997 Jun 15;126(12):1006.

Källén, B. 2003. Maternal Drug Use and Infant Cleft Lip/Palate With Special Reference to Corticoids.
The Cleft Palate-Craniofacial Journal: 40,(6): 624–628.

Kiersch TA, Halladay SC, Hormel PC. A single-dose, double-blind comparison of naproxen sodium, acetaminophen, and placebo in postoperative dental pain. *Clin Ther.* 1994 May-Jun;16(3):394-404.

Kiersch TA, Halladay SC, Koschik M. A double-blind, randomized study of naproxen sodium, ibuprofen, and placebo in postoperative dental pain. *Clin Ther.* 1993 Sep-Oct;15(5):845-54.

Killick S, Elstein M. Pharmacologic production of luteinized unruptured follicles by prostaglandin synthetase inhibitors. *Fertil Steril.* 1987 May;47(5):773-7.

Klassen DK, Jane LH, Young DY, Peterson CA. Assessment of blood pressure during naproxen therapy in hypertensive patients treated with nicardipine. *Am J Hypertens.* 1995 Feb;8(2):146-53.

Kovacevic L, Bernstein J, Valentini RP, Imam A, Gupta N, Mattoo TK. Renal papillary necrosis induced by naproxen. *Pediatr Nephrol.* 2003 Aug;18(8):826-9.

Kulling PE, Backman EA, Skagius AS, Beckman EA. Renal impairment after acute diclofenac, naproxen, and sulindac overdoses. *J Toxicol Clin Toxicol.* 1995;33(2):173-7.

Levin GM, Grum C, Eisele G. Effect of over-the-counter dosages of naproxen sodium and acetaminophen on plasma lithium concentrations in normal volunteers. *J Clin Psychopharmacol.* 1998 Jun;18(3):237-40.

Lewis JD, Kimmel SE, Localio AR, Metz DC, Farrar JT, Nessel L et al. Risk of Serious Upper Gastrointestinal Toxicity With Over-the-Counter Nonaspirin Nonsteroidal Anti-inflammatory Drugs. *Gastroenterology.* 2005 Dec;129(6):1865-1874.

Lewis RV. Severe asthma after naproxen. *Lancet.* 1987 May 30;1(8544):1270.

Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ.* 2003 Aug 16;327(7411):368.

Londino AV Jr, Wolf GL, Calabro JJ, Perrone SJ. Naproxen and pneumonitis. *JAMA.* 1984 Oct 12;252(14):1853.

Maerker JM, Harm A, Foeldvari I, Hoger PH. Naproxeninduzierte Pseudoporphyrie. *Hautarzt.* 2001;52:1026-1029.

Manoukian AV, Carson JL. Nonsteroidal anti-inflammatory drug-induced hepatic disorders. Incidence and prevention. *Drug Saf.* 1996 Jul;15(1):64-71.

McKinnon BJ, Lassen LF. Naproxen-associated sudden sensorineural hearing loss. *Mil Med.* 1998 Nov;163(11):792-3.

McMahon AD, Evans JM, MacDonald TM. Hypersensitivity reactions associated with exposure to naproxen and ibuprofen: a cohort study. *J Clin Epidemiol.* 2001 Dec;54(12):1271-4.

McNeil P, MacKenzie I, Manoharan A. Naproxen-associated aplastic anaemia. *Med J Aust.* 1986 Jul 7;145(1):53-5.

Meek IL, Vonkeman HE, Kasemier J, Movig KL, van de Laar MA. Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: a placebo-controlled, ex vivo, serial placebo-controlled serial crossover study. *Eur J Clin Pharmacol.* 2013;69:365-71.

Mendonca LL, Khamashta MA, Nelson-Piercy C, Hunt BJ, Hughes GR. Non-steroidal anti-inflammatory drugs as a possible cause for reversible infertility. *Rheumatology (Oxford).* 2000 Aug;39(8):880-2.

Methotrexate Drugdex Micromex 2004

Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Saf.* 2002;25(5):345-72.

Mordes JP, Johnson MW, Soter NA. Possible naproxen-associated vasculitis. *Arch Intern Med.* 1980 Jul;140(7):985.

Nadell J, Bruno J, Varady J, Segre EJ. Effect of naproxen and of aspirin on bleeding time and platelet aggregation. *J Clin Pharmacol.* 1974 Apr;14(4):176-82.

Nicastro NJ. Visual disturbances associated with over-the-counter ibuprofen in three patients. *Ann Ophthalmol.* 1989 Dec;21(12):447-50.

Nielsen GL, Sorensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ.* 2001 Feb 3;322(7281):266-70.

Non-steroidal anti-inflammatory drugs and serious gastrointestinal adverse reactions--2. *Br Med J (Clin Res Ed).* 1986 May 3;292(6529):1190-1.

Nygaard N, Starkebaum G. Naproxen and agranulocytosis. *JAMA.* 1987 Apr 3;257(13):1732.

Ogawa H, Kurashima K, Namura M, Kanaya H, Kawamura Y, Ohka T et al. Pulmonary infiltrates with eosinophilia due to naproxen. *Jpn J Med.* 1991 Jan-Feb;30(1):32-4.

Oldenhof J, Hochberg M, Schiff M, Brune K. Effect of maximum OTC doses of naproxen sodium or acetaminophen on low-dose aspirin inhibition of serum thromboxane B2. *Curr.Med. Res. Opin.* 2010; 26 (6): 1497-1504 Ostensen M, Villiger PM. Nonsteroidal anti-inflammatory drugs in

systemic lupus erythematosus. *Lupus*. 2001;10(3):135-9.

Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an under recognized public health problem. *Arch Intern Med*. 2000 Mar 27;160(6):777-84.

Pai S, Marinkovich MP. Epidermolysis bullosa: new and emerging trends. *Am J Clin Dermatol*. 2002;3(6):371-80.

Patrono C, Ciabattini G, Patrignani P, Pugliese F, Filabozzi P, Catella F, Davì G, Forni L. Clinical pharmacology of platelet cyclooxygenase inhibition. *Circulation*. 1985;72:1177-84.

Perez Gutthann S, Garcia Rodriguez LA, Raiford DS, Duque Oliart A, Ris Romeu J. Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure. *Arch Intern Med*. 1996 Nov 25;156(21):2433-9.

Perez-Gutthann S, Garcia-Rodriguez LA, Duque-Oliart A, Varas-Lorenzo C. Low-dose diclofenac, naproxen, and ibuprofen cohort study. *Pharmacotherapy*. 1999 Jul;19(7):854-9.

Petersen B, Brune K, Burkhard Hinz E. Naproxen sodium, for the treatment of mild to moderate pain: experience in medical and pharmaceutical practice. *DAZ*. 2002;18:271-275.

Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med*. 1991 May 1;114(9):735-40.

Probst L, Stoney P, Jeney E, Hawke M. Nasal polyps, bronchial asthma and aspirin sensitivity. *J Otolaryngol*. 1992 Feb;21(1):60-5.

Pullar T, Capell HA. Interaction between oral anti-coagulant drugs and non-steroidal anti-inflammatory agents: a review. *Scott Med J*. 1983 Jan;28(1):42-7.

Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. *J Clin Psychopharmacol*. 1986 Jun;6(3):150-4.

Rao GH, Johnson GG, Reddy KR, White JG. Ibuprofen protects platelet cyclooxygenase from irreversible inhibition by aspirin. *Arteriosclerosis*. 1983;3:383-388.

Ravi S, Keat AC, Keat EC. Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J*. 1986 Aug;62(730):773-6.

Renschler H, Schaeffer A, Tholan H, Voegtli J. [Genesis of interstitial nephritis.] *Schweiz Med Wochenschr*. 1956 Sep 1;86(35):978-81.

Roe RL, Ellis DJ, Bruno JJ. Effect of naproxen on platelet function in male and female subjects. *Clin Res*. 1980;28:322a.

Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T et al. Medication use and

the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995 Dec 14;333(24):1600-7.

Runkel R, Chaplin M, Boost G, Segre E, Forchielli E. Absorption, distribution, metabolism, and excretion of naproxen in various laboratory animals and human subjects. *J Pharm Sci.* 1972 May;61(5):703-8.

Runkel R, Chaplin MD, Sevelius H, Ortega E, Segre E. Pharmacokinetics of naproxen overdoses. *Clin Pharmacol Ther.* 1976 Sep;20(3):269-77.

Runkel R, Mroszczak E, Chaplin M, Sevelius H, Segre E. Naproxen-probenecid interaction. *Clin Pharmacol Ther.* 1978 Dec;24(6):706-13.

Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH- Sodium Collaborative Research Group. *N Engl J Med.* 2001 Jan 4;344(1):3-10.

Saker BM, Kincaid-Smith P. Papillary necrosis in experimental analgesic nephropathy. *Br Med J.* 1969 Jan 18;1(5637):161-2.

Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol.* 1995 Mar;35(3):209-19.

Schapira D, Balbir-Gurman A, Nahir AM. Naproxen-induced leukocytoclastic vasculitis. *Clin Rheumatol.* 2000;19(3):242-4.

Schiff M, Minic M. Comparison of the analgesic efficacy and safety of nonprescription doses of naproxen sodium and Ibuprofen in the treatment of osteoarthritis of the knee. *J Rheumatol.* 2004 Jul;31(7):1373-83.

Schmidt LE, Dalhoff K. Food-drug Interactions. *Drugs.* 2002;62(10):1481-502.

Seaton RA, France AJ. Recurrent aseptic meningitis following non-steroidal anti-inflammatory drugs-a reminder. *Postgrad Med J.* 1999 Dec;75(890):771-2.

Segre EJ. Naproxen sodium (Anaprox): pharmacology, pharmacokinetics and drug interactions. *J Reprod Med.* 1980 Oct;25(4 Suppl):222-5.

Sevelius H, Runkel R, Segre E, Bloomfield SS. Bioavailability of naproxen sodium and its relationship to clinical analgesic effects. *Br J Clin Pharmacol.* 1980 Sep;10(3):259-63.

Sheehan NJ. Pulmonary infiltrates and eosinophilia associated with naproxen. *Br J Rheumatol.* 1985 Aug;24(3):302-3.

Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Arch Intern Med.* 1993 Jul 26;153(14):1665-70.

Simon LS, Basch CM, Young DY, Robinson DR. Effects of naproxen on renal function in older patients with mild to moderate renal dysfunction. *Br J Rheumatol*. 1992 Mar;31(3):163-8.

Singh RR, Malaviya AN, Pandey JN, Guleria JS. Fatal interaction between methotrexate and naproxen. *Lancet*. 1986 Jun 14;1(8494):1390.

Slattery JT, Levy G, Jain A, McMahon FG. Effect of naproxen on the kinetics of elimination and anticoagulant activity of a single dose of warfarin. *Clin Pharmacol Ther*. 1979 Jan;25(1):51-60.

Smith G, Roberts R, Hall C, Nuki G. Reversible ovulatory failure associated with the development of luteinized unruptured follicles in women with inflammatory arthritis taking non-steroidal anti-inflammatory drugs. *Br J Rheumatol*. 1996 May;35(5):458-62.

Spence JD. Influence of non-steroidal anti-inflammatory drugs on the blood-pressure-reducing effects of enalapril and nifedipine. *J Hypertens*. 1996 Jan;14(1):145.

Stewart CF, Fleming RA, Arkin CR, Evans WE. Coadministration of naproxen and low-dose methotrexate in patients with rheumatoid arthritis. *Clin Pharmacol Ther*. 1990 Apr;47(4):540-6.

Stone S, Khamashta MA, Nelson-Piercy C. Nonsteroidal anti-inflammatory drugs and reversible female infertility: is there a link? *Drug Saf*. 2002;25(8):545-51.

Strom BL, Schinnar R, Bilker WB, Feldman H, Farrar JT, Carson JL. Gastrointestinal tract bleeding associated with naproxen sodium vs ibuprofen. *Arch Intern Med*. 1997 Dec 8-22;157(22):2626-31.

Sylvia LM, Forlenza SW, Brocovich JM. Aseptic meningitis associated with naproxen. *Drug Intell Clin Pharm*. 1988 May;22(5):399-401.

Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G, Pieton R. Asthmatic attacks induced in aspirin-sensitive patients by diclofenac and naproxen. *Br Med J*. 1977 Jul 23;2(6081):231-2.

Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol*. 1977 Nov;60(5):276-84.

Szmyd L Jr, Perry HD. Keratopathy associated with the use of naproxen. *Am J Ophthalmol*. 1985 May 15;99(5):598.

Todd PA, Clissold SP. Naproxen. A reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. *Drugs*. 1990 Jul;40(1):91-137.

Tomlinson RV, Ringold HJ. Relationship between inhibition of prostaglandin synthesis and drug efficacy: support for the current theory on mode of action of aspirin-like drugs. *Biochem Biophys Res Commun*. 1972 Jan 31;46(2):552-9.

Trechot P, Gillet P, Gay G, Hanesse B, Netter P, Castot A, Larrey D. Incidence of hepatitis induced by non-steroidal anti-inflammatory drugs (NSAID). *Ann Rheum Dis.* 1996 Dec;55(12):936.

Vale JA, Meredith TJ. Acute poisoning due to non-steroidal anti-inflammatory drugs. Clinical features and management. *Med Toxicol.* 1986 Jan-Feb;1(1):12-31.

van Puijenbroek EP, Egberts AC, Heerdink ER, Leufkens HG. Detecting drug-drug interactions using a database for spontaneous adverse drug reactions: an example with diuretics and non-steroidal anti-inflammatory drugs. *Eur J Clin Pharmacol.* 2000 Dec;56(9-10):733-8.

van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG. Different risks for NSAID-induced anaphylaxis. *Ann Pharmacother.* 2002 Jan;36(1):24-9.

Veal GJ, Back DJ. Metabolism of Zidovudine. *Gen Pharmacol.* 1995 Nov;26(7):1469-75.

Walker AM. Quantitative studies of the risk of serious hepatic injury in persons using nonsteroidal antiinflammatory drugs. *Arthritis Rheum.* 1997 Feb;40(2):201-8.

Weber SS, Bankhurst AD, Mroszczak E, Ding TL. Effect of Mylanta on naproxen bioavailability. *Ther Drug Monit.* 1981;3(1):75-83.

Weitz JI. Blood Coagulations and Anticoagulant, Fibrinolytic, and Antiplatelet Drugs. Goodman and Gilman's: The Pharmacological Basis of Therapeutics. Lawrence L Brunton. 12th ed. McGraw Hill. New York. 2011.

Weksler BB, Lehany AM. Naproxen-induced recurrent aseptic meningitis. *DICP.* 1991 Nov;25(11):1183-4.

Whiting B, Williams RL, Lorenzi M, Varady JC, Robins DS. Effect of naproxen on glucose metabolism and tolbutamide kinetics and dynamics in maturity onset diabetics. *Br J Clin Pharmacol.* 1981 Mar;11(3):295-302.

Winder CV, Welford M, Wax J, Kaump DH. Pharmacologic and toxicologic studies of m-(1-methyl-3-propyl-3-pyrrolidiny)phenol (CI-572), an analgetic and antitussive agent. *J Pharmacol Exp Ther.* 1966 Oct;154(1):161-75.

Woodard, G., Post, K.F., Cockerell, K.O. & Cronin, M.T.I., *Toxic. Appl. Pharmacol.* 7:503 (1965).

Wright MS. Drug-induced hemolytic anemias: increasing complications to therapeutic interventions. *Clin Lab Sci.* 1999 Mar-Apr;12(2):115-8.

Product Monograph – ALEVE® (Naproxen Sodium Tablets USP 220 mg) ALEVE® Liquid Gels (Naproxen Sodium Capsules 220 mg), ALEVE® Back and Body Pain (Naproxen Sodium Capsules 220 mg) Bayer Inc.. Date of Revision: May 29, 2020, Control No. 237829.

PART III: CONSUMER INFORMATION

**NAPROXEN SODIUM CAPSULES
220 mg**

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

What dosage forms it comes in:

Capsule: 220 mg

WARNINGS AND PRECAUTIONS

Stomach bleeding warning: This may cause stomach bleeding. Symptoms may include: feeling faint, vomiting blood, bloody or black stools.

- 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

BEFORE you use NAPROXEN SODIUM CAPSULES talk to your doctor or pharmacist if you have or have had:

- asthma or a similar respiratory illness
- nasal polyps
- itchy skin and hives
- history of gastrointestinal disease
- high blood pressure
- a blood clotting disorder
- heart disease/failure
- any other serious disease

OR if you are:

- trying to conceive
- in your first or second trimester of pregnancy
- nursing
- taking any other drug

When using this product:

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

Stop use and ask a doctor if:

- fever lasts more than 3 days
- pain lasts more than 5 days
- symptoms get worse or new ones appear

INTERACTIONS WITH THIS MEDICATION

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.

ABOUT THIS MEDICATION

What the medication is used for:

Trust NAPROXEN SODIUM CAPSULES for providing fast and effective relief of pain such as arthritis pain and pain of inflammation. NAPROXEN SODIUM CAPSULES relieves arthritic conditions such as stiffness, pain experienced day or night due to arthritis or stiffness of rheumatic conditions. NAPROXEN SODIUM CAPSULES also relieves joint and body pain, muscular ache, muscle sprains and strains, backache, minor aches, headaches, migraine pain, menstrual cramps, pain of minor surgery, toothaches, pain of dental extractions, pain associated with the common cold and reduces fever. Clinical studies show long lasting relief for up to 12 hours.

What it does:

NAPROXEN SODIUM CAPSULES is a pain reliever and fever reducer.

NAPROXEN SODIUM CAPSULES works both at the site of pain and in your central nervous system. NAPROXEN SODIUM CAPSULES starts to work fast and treats pain where it starts.

When it should not be used:

Do not take NAPROXEN SODIUM CAPSULES if you:

- are allergic to naproxen, naproxen sodium, or any ingredient in the formulation
- are allergic to acetylsalicylic acid (ASA), other salicylates or other non-steroidal anti-inflammatory drugs (NSAIDs)
- have an active peptic ulcer, a history of recurrent ulceration, or active gastrointestinal bleeding
- have inflammatory bowel disease
- have liver disease (active or severe)
- have kidney disease (severe or worsening)
- are in your third trimester of pregnancy
- are right before or after heart surgery

What the medicinal ingredient is:

Naproxen sodium 220 mg

What the important non-medicinal ingredients are:

ammonium hydroxide, FD&C Blue #1, gelatin, glycerine, high polychains, lactic acid, mannitol, polyethylene glycol, povidone, propylene glycol, purified water, shellac, simethicone, sorbitol sorbitan, titanium dioxide

IMPORTANT: PLEASE READ

BEFORE you use NAPROXEN SODIUM CAPSULES talk to your doctor or pharmacist if are taking any other drug especially:

- Anticoagulants (to decrease blood clotting)
- Antihypertensive drugs for your heart (including ACE inhibitors and beta-blockers)
- Diuretics (“water pills”)
- Cyclosporine
- Glucocorticoids
- Lithium
- Methotrexate
- Low dose ASA for doctor supervised daily preventive therapy (e.g. acetylsalicylic acid 81 mg)
- NSAIDs or other pain medications (e.g. ibuprofen, acetaminophen)

Taking NAPROXEN SODIUM CAPSULES with a meal will delay its absorption.

PROPER USE OF THIS MEDICATION

Usual dose:

Adults (12 to 65 years): 1 capsule every 8 to 12 hours. Adults over 65 years 1 capsule every 12 hours. Do not take more than 2 capsules in a 24 hour period. Drink a full glass of water with each dose. Do not use in children under 12 years.

Overdose:

If you think you have taken too much Naproxen Sodium Capsules contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, NAPROXEN SODIUM CAPSULES 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, diarrhea or constipation.

This is not a complete list of side effects. For any unexpected effects while taking NAPROXEN SODIUM CAPSULES, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Stop use and get emergency medical attention IMMEDIATELY if you experience: difficulty breathing, facial swelling, hives, rash or itching.

Stop use and contact a doctor or pharmacist if you experience: black stools, severe abdominal pain, any change in vision or fluid retention.

If you become drowsy, dizzy or lightheaded do not drive or operate

machinery and contact your doctor or pharmacist.

HOW TO STORE IT

● **CAUTION:** This package contains enough drug to seriously harm a child. Keep out of children’s reach.

Store at 15°C to 25°C, avoid high humidity and excessive heat over 40°C.

REPORTING SUSPECTED SIDE EFFECTS

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

- Visiting the Web page on [Adverse Reaction Reporting \(https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html\)](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.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.

MORE INFORMATION

If you want more information about Naproxen Sodium Capsules:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>). Find the Consumer Information on the manufacturer’s website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: October 14, 2020