Diphenhydramine Hydrochloride
Plasma concentrations of diphenhydramine appear to decline in a monophasic manner, although some pharmacokinetic data suggest a polyphasic elimination. The terminal half-life of diphenhydramine has not been fully elucidated, but appears to range from 2.4-9.3 hours in healthy adults. The terminal elimination half-life reportedly is prolonged in adults with liver cirrhosis.

Following oral administration of a single 100 mg dose of diphenhydramine in healthy adults, about 50-75% of the dose is excreted in the urine in 4 days, almost completely as metabolites and with most urinary excretion occurring within the first 4-48 hours. Only about 1% of a single oral dose is excreted unchanged in the urine.

The total body clearance of diphenhydramine decreases with age. For example, after a single 1.25 mg/kg oral (syrup) dose, the total body clearance for the elderly and children were 11.7 ± 3.1 mL/min/kg versus 49.2 ± 22.8 mL/min/kg, respectively.

The elimination half-life of diphenhydramine is prolonged with age. After a single dose administration of diphenhydramine syrup 1.25 mg/kg, elderly patients exhibited a mean half-life of 13.5 hours compared with 9.2 hours in young adults and 5.4 hours in children.

Special Populations and Conditions

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

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 between 15 - 30°C.

SPECIAL HANDLING INSTRUCTIONS

No special requirements

DOSAGE FORMS, COMPOSITION AND PACKAGING

One caplet of ALEVE Nighttime contains naproxen sodium 220 mg, of which 20 mg is sodium

and diphenhydramine hydrochloride 25mg. The excipients consist of carnauba wax, FD&C Blue #2 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, talc, and titanium dioxide.

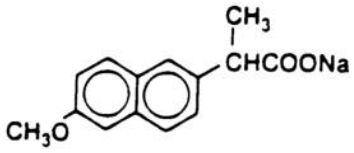
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Naproxen Sodium

Proper name: Naproxen sodium
Chemical name: 2-Napthaleneacetic acid, 6-methoxy –α -methyl-, sodium salt, (-).
Molecular formula and molecular mass: $C_{14}H_{13}NaO_3$, 252.24
Structural formula:



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

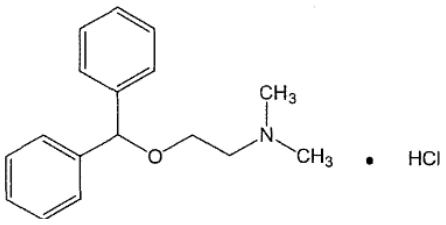
Diphenhydramine Hydrochloride [130]

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

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 167º-172ºC.

CLINICAL TRIALS

Studies with Naproxen Sodium

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

Studies with Diphenhydramine Hydrochloride (DPH)

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

Studies with Naproxen Sodium and Diphenhydramine Hydrochloride

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

Study demographics and trial design

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

Study Results

Table 4: Summary of Patient Demographics for Pivotal Clinical Trial

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

Table 5: Overview of Pivotal Clinical Trial Result						
Study	**Endpoints**	**Associated values and statistical significance for ALEVE Nighttime (A), ALEVE (B) and DPH (C)**				
		ALEVE Nighttime	**ALEVE**	**DPH**	**A vs. B**	**A vs. C**
Buchanan 14837	Wake After Sleep Onset (mean)	142.2	214.3	429.5	0.0002	< 0.0001
	Sleep Latency (median)	25.50	25.75	41.50	NS	< 0.0001
	Total Sleep Time (mean)	427.7	355.6	143.2	0.0001	-----
	Sleep Efficiency (mean)	71.3	59.3	23.9	0.0007	-----
	Sleep Quality (mean)[1]	2.1	1.4	1.7	< 0.0001	0.0494
	Pain Intensity[2] (LS-mean)	-1.2	-0.9	0.1	0.0064	< 0.0001
	Pain Relief[3] (mean)	2.4	2.0	0.6	0.0047	< 0.0001
	Subjective Assessment of Pain Relief[4] (mean)	2.9	2.8	1.8	0.2734	< 0.0001
	Proportion Taking Rescue Medication (%)	18.7	27.1	49.0	0.0053	< 0.0001

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

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

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

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

Pivotal Comparative Bioavailability Study

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

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

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

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

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

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

DETAILED PHARMACOLOGY

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

TOXICOLOGY

Naproxen Sodium

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

Subacute and Chronic Oral Studies

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

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

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

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

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

A wide range of susceptibility to gastrointestinal lesions from administration of naproxen was evident in the various species tested. For example, 30mg/kg/day was tolerated well by rats for 90 days, but the same dose was ulcerogenic when administered for 6 months. Rhesus monkeys and miniature swine exhibited no significant pathology when dosed with naproxen at 45 mg/kg/day

for 30 days. This dose of naproxen was also tolerated by miniature swine without obvious evidence of adverse effects when administered daily for 1 year. In rhesus monkeys doses as high as 120 mg/kg/day (60 mg/kg b.i.d.) for 6 months produced no clinical or histopathological evidence of gastrointestinal irritation although occult blood in the feces occurred more frequently in these animals compared to controls. Daily administration of naproxen to rhesus monkeys for one year was associated with mild gastric irritation in a few animals receiving 100, 140 or 180 mg/kg. In rabbits the maximum tolerated repeated oral dose is 80 to 100 mg/kg/day. Mice survived oral daily doses of 240 mg/kg/day for 6 months. In dogs, on the other hand, 5.0 mg/kg/day approaches the maximum tolerated dose. This peculiar canine susceptibility to gastrointestinal effects of non-steroidal anti-inflammatory agents has also been shown with indomethacin and ibuprofen.

In dogs naproxen exhibits a considerably longer plasma half-life than it does in rats, guinea pigs; miniature swine, monkeys, and man. The same observation has been made with ibuprofen in dogs compared to rats and man. In addition, in the species listed, only the dog excretes significant amounts of administered naproxen in the feces (50%). In the rat, guinea pigs, miniature swine, monkey and man, 86-90% of the administered drug is excreted in the urine. The suggested enteroheptic 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.

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 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.

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.

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